UNIVERSITY OF TORONTO MEDICAL JOURNAL

FEATURE ARTICLE

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VOLUME XXXIX
NUMBER 5
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THE COVER

Leonard Thompson (see page 189), as he appears in an old photograph discovered in the Banting archives. In reference to Dr. Walter Campbell's feature article *Anabasis,* this fortunate teenager seems to perceive the Toronto hoplites (ὁπλιτης), armed with knowledge and perseverance, struggling to discover a medical paradise (παραδεισος). *Anabasis* means "a going up out of". Little perhaps did Leonard Thompson realize that his success elevated the spirits of medical men and their diabetic patients the world over.

W.S.C.

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Editorial

An Approach We Have Lost

It is often interesting and at times amusing to read the writings of great physicians of the past, but for those with the patience to indulge in discovery of ideas a careful perusal of such writings usually results in an exhilarating adventure of the mind. Such were the experiences of Osler, Penfield and many other pillars of our profession in this century on discovering a *philisophy for physicians* in Sir Thomas Browne's work entitled *Religio Medici.*

The relevance of a seventeenth century physician's ideas today is in itself astounding. This is particularly true if we bear in mind that he wrote for another era, in which physical conflict dominated the interest of the masses and manifested itself at all levels of life. Passion was the driving force in politics, professional activities, private affairs and religion (where this passion, coupled with theological dogma, eclipsed practical faith).

Three centuries later we find ourselves at another extreme. Our conflicts are now ideological. Technology and the pursuit of knowledge appear to be motivated only by "Comfort Above All", the motto of our civilization. Reason is our only god at whose feet we have sacrificed practical faith.

The medical profession has also been engulfed by these trends. We are in the thick of the battle between socialism and individualism. If our motives are sound this is desirable no matter what we believe is right. All too often, however, our motives are subject to "comfort above all". This, I believe is also at the root of problems of manpower shortage in the fields of general practice, university teaching, research, service in underdeveloped nations and other realms of medical work that demand personal sacrifice. The importance of understanding the disease process has taken precedence over the importance of understanding the *diseased person.* The dazzling god of reason has made us blind to the fact that we deal daily with men on their deathbeds; only faith is vital to them, not the rationale of narcotic administration. In summary, society as a whole and our profession in particular are as lopsided to-day as they were three hundred years ago.

A brilliant observer, Sir Thomas realized that man is innately an unbalanced creature. He grasped the problems of humanity and expounded them in his book. In devoting a great part of his work to solutions, he could well be called the Apostle of Equilibrium. A typical statement which summarises well the essence of his thought follows:

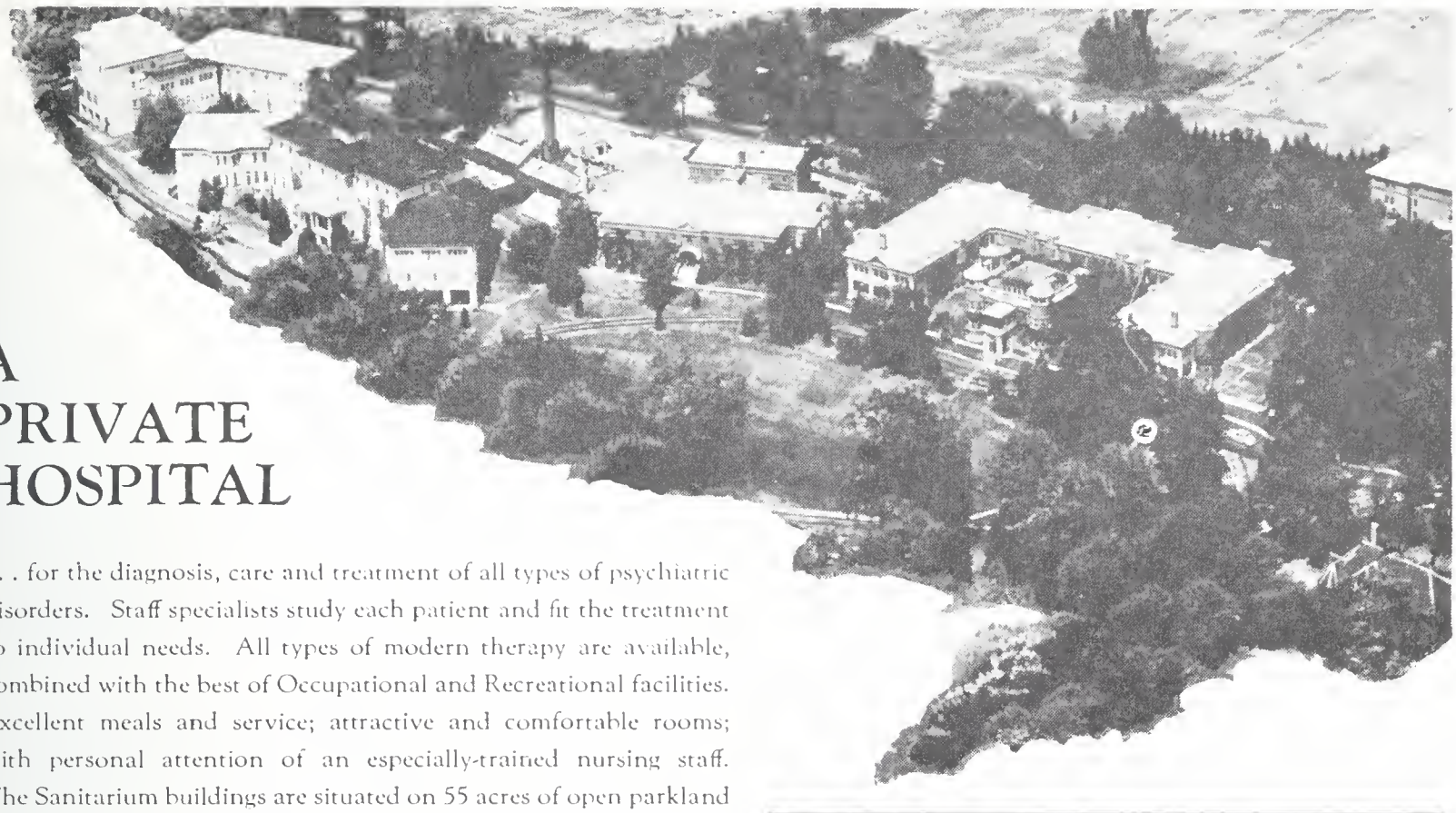
> ". . . there is in our soul a kind of Triumvirate, or triple government of three Competitors, which distract the Peace of this our Commonwealth, not less than it did that other, the State of Rome.
>
> As Reason is a Rebel unto Faith, so Passion unto Reason: as the propositions of Faith seem absurd unto Reason, so the Theorems of Reason unto Passion, and both unto Reason. Yet a moderate and peacable discretion may so state and order the matter that they may all be Kings and yet make but one Monarchy."

We consider it desirable to focus our minds on Sir Thomas' plea for equilibrium to the medical profession of his age and ours. If we are to maintain our position of leadership in society our approach to medicine as a cold pure science must cease. Our rejection of the arts and letters must disappear. Our scoffing at religion must become outdated. Lastly, we must acquire a new realization of the intrinsic value of each individual who choses us to be his physician.

The arch-skeptic George Bernard Shaw, the nineteenth century materialist *par excellence* realized also, when he had lived a full measure of years, that there are values in life that are beyond the scales of science:

> "There is nothing that people will not believe nowadays if only it be presented to them as science, and nothing they will not disbelieve if it be presented to them as religion. I myself began like that; and I am ending by receiving every scientific statement with dour suspicion whilst giving every respectful consideration to the inspiration of the prophets and poets."

We should be the first ones to agree. W.O.S.



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The Early Clinical Use of Insulin

by Lillian A. Chase, B.A., M.B.

Forty years ago, in the winter of 1922, Professor McPhedran presented to his fifth year class, of which I was a member, a little diabetic boy, who, in addition to the usual diabetic treatment, had had two doses of "Banting's fluid".

This fourteen year old boy had had diabetes for two years, weighed 65 pounds on admission. His blood sugar was 580 mg %; he was kept alive on a diet of 450 calories. Admitted to the Toronto General Hospital on December 2, 1921, he was rapidly getting worse. On January 11, 1922 he was given the pancreatic extract. The first dose was 15 c.c. Leonard Thompson lived fifteen more years and died of unrelated bronchopneumonia in 1937 at the age of 29.

Toronto was prepared to use the hormone because in 1915 Dr. William Goldie had asked Dr. Walter Campbell to start an Out-Patient Diabetic Clinic at the Toronto General. This was the first in Canada. It suffered a staff shortage while Dr. Campbell was overseas with the CAMC in Basingstoke but was at full strength again when he returned.

When insulin became available for clinical use it was given to Dr. Campbell and his colleague, Dr. Almon Fletcher, to administer to the patient who needed it most. The first published report of its clinical effect appeared under both names as well as those of Banting, Best and Collip.

In the spring of 1922 Eli Lilly and Company had come into the picture. Their knowledge of large-scale production was put at the disposal of the University of Toronto. Mr. (later Dr.) C. H. Best, B.A., spent the year 1922-23 on the problem of mass production of insulin, and that same year he did his M.A. thesis.

By July and August of 1922 Eli Lilly was supplying insulin to Banting and his associates. That summer one or two hundred units meant a great deal to Banting and his patients. Lilly's also provided insulin to diabetic specialists in the United States: among those supplied were Joslin of Boston, Williams of Rochester, Woodyatt of Chicago, and Wilder of the Mayo Clinic. On August 7, 1922 Joslin administered his first dose of insulin to a nurse who had lived five years with her diabetes. Her weight had fallen from 157 to 72 pounds but she had remained sugar free.

By autumn of 1922 thousands of units became available and early in 1923 all the insulin necessary for clinical treatment was produced, but was still restricted by the Toronto Insulin Committee to a limited number of institutions and individuals who had experience in its use.

Later it was entrusted to one doctor in a centre who had been designated by his colleagues as capable of handling this powerful agent. Fear of hypoglycemia was very real.

Patients came to Banting from all over the world. These patients were looked after in the Private Patients Pavilion. Treatment was expensive as insulin cost five cents a unit. After the hormone became widely available, Banting dropped his practice and went back to the laboratory.

Dr. Campbell and Dr. Fletcher were in charge of the public ward patients and also had private patients. Every patient who got insulin was put in hospital to become standardized. At the Hospital for Sick Children Dr. Gladys Boyd was in charge of the diabetic children. Other doctors did not use insulin because they did not know how to regulate the dose.

When the medical internes came on duty in July 1923 we were given three lectures on diabetes by Dr. Campbell and three by Dr. Fletcher. When we had completed this course we knew more about insulin and its action than any other internes anywhere in the world.

The Toronto General Hospital atmosphere throbbed with excitement; anything we were asked to do for a diabetic was a privilege, not a duty, whether it was taking blood sugars every two hours round the clock or doing a glucose tolerance test on Christmas morning, it was all part of our contribution to knowledge. Neither clock nor calendar deterred Dr. Campbell from his purpose. Convinced of the value of the person-to-person method of teaching, he was never hurried or superficial in his explanations.

Dr. Campbell encouraged an interest in diabetics which inspired more than one of his house staff to carry on indefinitely among the people afflicted by the genetic defect that insulin alleviates.

feature article -

Anabasis

by Walter Campbell, M.A., M.D., F.R.C.P.(C), F.R.S.C.

I take the title from Xenophon and Almon Fletcher will hear the heavy tread of the ὁπλιτης and πελταστης as they marched and fought over burning sands to παραδεισος, the king's park, and across snow-filled mountain passes up unto Trebizond on the Euxine Sea some 2400 years ago.

Anabasis, yes. This too is a travelogue — a travelogue back into time when we had no such thing as colour photography and the paintings were starkly impressionistic. With the years, the colours have faded somewhat; have become less garish and a rosy light illumines them. I think I would regret having them cleaned up as Rembrandt's "Night Watch" was cleaned up when it emerged from the caves after the war. It was wondrous fair before.

To go back fifty years, the professors received $2500 per year: we received $62.50 per month for eight months of the year. In the summer we were expected to hibernate and live on our fat. The Professor, Bert Collip and I constituted the full-time staff in Biochemistry and juniors in Physiology and Biochemistry doubled in brass for the other department. Thus we covered the Honour courses in the Arts Faculty, the medical students, the dental students and the veterinary science students. The Professor was not exactly idle either. Besides giving the lectures in Biochemistry he also doubled in brass in World History, History of Medicine, Greek Architecture and Greek Sculpture and very interesting he was, too.

You might say that we were in somewhat straitened circumstances. Cats were worth 25 cents each and when I caught eight cats and five kittens in the barns of Welland County and carried them back with me on the Dalhousie City, they charged me fifty cents for transport. When I presented the bill to my professor he said, "Humph, when I was a young man I walked to Grenadier Pond and caught my own frogs." I think he would dearly have loved it if I had asked, "What was the biggest one you caught with those frogs?" but we wore stiff Christies, carried our tan gloves in our left hands on the coldest days and took off our hats to our professors; very proper young men and perhaps a little in awe of an F.R.S. "Andy" Macallum was a kindly man and he "spoke the Gaelic" of his fathers. But ironic humour is not confined to one tongue. *His* overflowed into precise and impeccable English. Well anyway, he paid the fifty cents, perhaps out of his own pocket.

Our professor could do quantitative urine sugars and four of us juniors learned and taught the method. It wasn't till late 1913 that I learned to do blood sugars and my professor learned with me. It wasn't the simple trick used today and previous methods were completely worthless.

In the summer of 1913, by grace of the Faculty, five of us did the work of the third year in medicine. Here I should like to pay tribute to our instructors, Dr. McPhedran, Dr. Goldie, Dr. Bob Armour, Dr. John Oille on the medical side, Mr. Cameron, Dr. Malcolm Cameron and Dr. Norman Shenstone on the surgical side, and Dr. J. J. Mackenzie, Dr. J. B. Leathes and Dr. Duncan Graham on the academic side. We lived right in the hospital and absorbed the teachings and techniques of our preceptors like sponges. One of them received a reward for that summer. Dr. Malcolm Cameron married Olive Gair Patterson after she graduated, and they became the parents of a handsome boy, afterwards a victim of paralytic polio, whose indomitable courage fills me with astonishment and admiration.

In 1913 I saw my first diabetics and it all came about because I could do quantitative analyses for sugar. Before the first war there were only two kinds of diabetics, those who died quick and those who stuck around for a long time. For the first group there was little or nothing one could do; the second type had certain inconveniences to put up with. In Europe they do some things better than we do, but we are still a young country, hardly civilized and certainly without culture. In Paris they tack a large, cylindrical sheet of galvanized iron eccentrically on the lamp poles. This is a convenience for some. Naunyn and Von Noorden removed the sugar and fancy Kuchen from the diet and substituted vegetables and that helped to reduce the inconvenience, in some cases markedly. Dr. Cameron had two stout old ladies on his visiting list and wished to help them and I agreed

to do the quantitative sugars. Well it worked, and soon we had only to do qualitative sugar tests to see if they had any sugar at all and finally I taught them to do their own tests. But this didn't stop my work, for other men on the Faculty let me help them, an honour and perhaps in a way some recompense for all they did for me. Then some new things happened in the diabetic world. Frederick M. Allen and others showed that by rigid dietary restriction a larger and larger proportion of diabetics could be helped and Joslin took it up. I graduated M.B. in '15 and immediately started a clinic for diabetes in our Out-Patient Department. One of my first patients was a Mr. Linder, a grocer out Parkdale way. I starved him sugar-free and gradually increased his diet. In spite of severe restrictions he was most faithful. His wife was also and undoubtedly helped him enormously. He was grateful too. I was living in the hospital, supervising the final year students who were acting as internes. I went home one night to learn that he had found out our address and delivered a whole case of canned peaches to my mother. He died in 1926 of leukemia, the first case I ever saw with the cutaneous manifestations. His poor wife came to my office some time later with a huge ulcerating mass in her right breast and glands in her axilla. Some one was treating her with arsenic paste. Too bad I was thought of as a specialist who knew nothing but diabetes. Roscoe Graham operated but she didn't live very long.

During the early part of the war I encountered my first case of renal glycosuria. He was invalided home with 100% disability as a diabetic and so he remained for more than twenty years. Renal glycosuria was not one of the 603 things you could have in the Army.

After the Armistice Colonel Graham was made the first full-time Professor of Medicine in the British Empire, and he offered me a job to come back home and help with the chemical and metabolic problems in Toronto General Hospital. The work was interesting and soon I had plenty of diabetics on Ward H. Miss Rosabel Coutts was a most excellent head nurse. We had no dietitian but she had a remarkable memory and a flair for mathematics and she took over the job of writing out diabetic diets from the prescription and this was a tremendous help. We were using a modified Allen treatment to desugarise them and followed this by a modified Woodyatt formula with increases above basal requirements to rehabilitate them. There was a lot to learn and the variations and combinations with other diseases made interesting problems to cope with.

During the summer of twenty-one we heard rumours of what Banting and Best were doing and I saw a little of it. The middle of November, just about this time, they put on a full dress exhibition of their results which left no question that the pancreatic extract must be tried on human diabetics and so we prepared for the experiment. There was a lot the physiology department did not know as yet and still more that we did not know. I thought it should be tried on the most severe cases we could find for two reasons. If nothing of value happened their number was up anyway and, more important, if effective in such patients, the results could not be gainsaid. We were already aware of what suitably restricted diets could do to diabetics of considerable severity, insulin must do something more. Well it did.

One evening "Les" Skeeles called me up. He recalled that we had been together at Basingstoke, and so on, so I knew he had a problem. He really had. A small boy weighing but 65 pounds had diabetes for a year and had become quite intractable to treatment, and he wanted me to take over. I told him if the boy was fourteen I thought I had pull enough to get him in. The problem of hospital admission was the same as today. Anyway we got Leonard Thompson in and found him quite as unresponsive to treatment as "Les" had said, so I told his father that the result was inevitable unless this new extract of Banting and Best could help his boy. He consented to the trial and the rest is history. He died thirteen years later of bronchopneumonia.

When we set out to the land of Cathay like the early explorers, we knew much, but much we knew was wrong. The various bays, gulfs and inlets we explored ended so often in a barrier of everlasting ice. Gradually the route in those uncharted seas has become clearer and today is dull routine and much less interesting. Today, the ship steams through the Northwest Passage and the atomic submarine glides safely under the polar ice. But not then. Control of diabetes, the conquest of acidosis, safeguarding the patient through surgical operations, and the rehabilitation of the diabetic patient came slowly, and I can show you little that we might not do better today. But we were young, able to work, of a sure faith and a knowledge that it must be done and so it was. But perhaps I can show you some pictures of what happened along the way.

In April we published a paper in the Canadian Medical Association Journal jointly with our colleagues in Physiology and Pathological Chemistry. In May we went to the Association of American Physicians. In the discussion Woodyatt moved an unprecedented rising vote of thanks. We had it made. We were already convinced of course, but now it was accepted in America, though treated with cautious but courteous reserve in Britain and derided in Germany. Rollin T. Woodyatt was the respected intellectual giant among diabetic clinicians of his day. He lived in a small house with his mother in suburban Chicago. His uncle was the architect of that magnificent Lakefront Boulevard System and also a diabetic. He played a good game of golf and I should not say he was entirely a recluse but he much preferred his work and his scientific library. His mother called him Rol, and when I ventured to ask if I might call him Rollin, he looked at me for a moment and then said, "Yes, but no one ever has." He was wrong. There were many who had reason to call him this in their hearts, not least of all his patients in those dark days when diabetes was not a metabolic defect but a deadly disease.

Perhaps the greatest of his pupils, one of many who benefited from his instruction and a prince of a fellow, Russell M. Wilder, died last year. He was responsible for many advances including the first study of hyperinsulinism. We had the second case and Roscoe Graham cured it at a time when operations on the pancreas were rare and dangerous.

And after that the Deluge. Noah had his troubles but also compensations. Thousands on thousands were anxious to try the new remedy and nearly all suffering from the delusion that it was a sure cure. So much accumulated misery makes one sick at heart, but there was one compensation. Though we must reject most of them for the time, advising them to keep closely in touch with their doctors till more insulin could be manufactured, we could pick out the worst patients to treat because they needed help first and because they were the only ones useful in confirming our thesis. It was necessary to form a clinic with Professor Graham at the helm; Banting, Fletcher and I treating our individual patients both on Ward H and the second floor of the Pavilion, which we took over for patients paying their own way.

This is clinical reminiscence, therefore I shall say nothing of our academic confreres save to record our appreciation of their many kindnesses and forbearance, their willingness to discuss our problems and to communicate their most recent accomplishments, whether of a positive or negative character. The award of the Nobel Prize thrilled us greatly and the prompt and generous sharing of the credit with their confreres no less. Look them over and you will see the London Goldsmith's sign, the Hallmark of Quality.

But now I shall say something I could never say before, one of a few compensations for encountering the nostalgia of 'once upon a time'. It is about Duncan Graham. A master tactitian, a superb strategist, his cool determination and incisive reasoning pulled us out of many difficulties. Except among the few who really know, few realize the part he played in the development of insulin. All of you will know and Canada will long benefit from his interest in Canadian Medicine. Few will realize his concern for the difficulties of the members of his staff. Only from personal experience and the confidences of long established friendships, do I know something of the many things made possible. I have known, though of course not intimately, almost all the great professors of medicine from Osler on down, and thus I can say, he was a great Professor of Medicine.

My classmate, Ed. Jeffrey, M.C. late D.A.D.M.S. London, was our field general and, as senior interne, actually injected the first pancreatic extracts. We could rely upon him for he was highly competent and he was up-to-date to the very minute as well as being the very human character you have known.

In this period too I am sorry to say, I learned a lesson — the lesson not to thank some people. After a weary night we were satisfied that our coma case would recover. Unthinkingly, I thanked the senior nurse and turned to leave — she burst into tears. She thought herself a part of the team and so she actually was. After that I didn't thank such people again. It may be that I have been rude — rude enough to pay some people a compliment they didn't deserve, but I think not. What we got from all sides was dedication, something far beyond professional competence, an emotional involvement which demanded of them as much as they could possibly give. But I believe in competence too. Our technicians were competent, honest and reliable. The programme owes a great deal to the sound training of our School of Household Science. I believe those girls must have eaten sometimes, but no one knows how often they took taxis home because it was dangerous to be out that early

in the morning. But the answers were there *on tap on time.*

Now I am not forgetting Almon though he has always been an enigma to me. He is over there and will speak for himself. You pose a problem, provide a little counter irritation and watch the ideas whiz around the convolutions, and he comes up with an answer and perfectly sound, too.

You know I have a dear friend who comes in from a golf game, tired and hungry, and, even before he showers, he orders a lettuce sandwich and devours the lettuce out of it. He says he just can't stop stuffing himself, and I have pleaded with him for years to try my minus a thousand calorie diet. Every dairy, every supermarket and every department store has a thousand calorie diet, and all are claimed to be different, but this one really is different. You don't wash it, you don't pare it, you don t boil it, you don't chew it, you don't swallow it, you don't digest it, it isn't hard on the kidneys and you don't pay for it. You just breath it in, free as the air. Every litre of oxygen when burned in the human body yields an average of 4.825 calories. Try it some time but out in the wild blue yonder. Beware of those evil carcinogens in city air.

O yes. Look! This is the picture of Lillian Chase. Lillian Chase sitting on a lab. table, kicking her heels against the locker doors and teaching eight year old Alvin K———— how to do his own blood sugars. "Tell me Dr. Chase, after you put the tungstic acid and everything into the blood, why does the blood turn to water when you put it in the paper in the funnel?" "Alvin," she said, "You are a dear little boy and I think you have learned enough for today." I haven't thanked her for she worked, nay slaved, with the rest.

Poor dwarfed, emaciated, pot-bellied Alvin. He had eaten enough grass to learn to produce cellulases and he had learned everything else about diabetes. An hour before I had stopped him from soliciting specimens from other patients. It interfered with our daily collections.

As you may suppose, we were flooded with visitors, many of them doctors with diabetes themselves. To all we tried to be kind but insulin was precious and hard to obtain. Most doctors with diabetes do not need insulin, most often they have the diabetes of the mature years. They need counselling and, if they would take as much care of themselves as they do of their patients, many would never need insulin. Their favourable economic status makes them vulnerable and their wives have often unwittingly contributed to their husbands having "a little sugar in the urine" as it is so commonly reported to them. Counsel their wives then that they boost his morale and help him to respect his limitations. If it becomes necessary, bluntly tell them that if they wish to enjoy the autumn years together then both must do their parts. A woman with any brains does not need to nag, they get their way by loving indirection and most of them know how.* Therefore, counsel their wives if you would like to see a lot of paunchy old friends grow old along with you. They will lose weight, of course, but that will relieve those arthritic joints and fallen arches and perhaps help their blood pressure. But we were talking about insulin. The delinquents are not too uncommon among doctors and diabetes may also develop in earlier years. You may remember best George Minot, a severe diabetic, only kept alive with insulin, until he had earned the secret of pernicious anaemia and the Nobel Prize for Medicine. In a world of unrest we talk much of security. In a way insulin is a security for you and for me who may one day get diabetes, and for countless others who now have a little sugar in the urine which still can be otherwise controlled, but who also stand in closer danger zones. This is not an unimportant aspect of insulin. But do not be misled into believing that insulin therapy is without its dangers. There is, for instance, no more pitiable spectacle than some patients who are given, sometimes unnecessarily, too much insulin and suffer mental deterioration. Insulin is a priceless boon to mankind, on many occasion actually life saving, and in many millions of other cases tranforms the unfortunate and despairing patient into a happy and self-respecting citizen. Just remember Joslin — who could have said it better? "Insulin is a remedy for the wise and not for the foolish, be they patients or doctors."

After this solemn and I hope, but do not believe, unnecessary preachment, may I put on another slide in our travelogue. Here is Henry Dale. He was sent from England to investigate the new discovery. A better choice could not have been made. In our years of association, though infrequent, I have never found anyone more kindly, not just merely kind, and so helpful. He was supremely competent and wise. He had no recent contact with clinical diabetes but that didn't matter. He had a mental capacity for outreaching many great men and he exercised it. I am sure

---

***What's so bad after all about a little mess of pottage if it makes the dear girl happy?**

Surgeon Captain Charlie Best, who knew him far better than I, will say "Aye aye, sir."

We were visited also by many famous clinicians. There is no pride of place or pomp among great teachers. We could talk with them and listen and learn. It was interesting when at last you got into bed and lay warming up those cool white sheets to recapture what you had learned that day, for we had much to learn.

Now there is the publisher, a brave and gallant gentleman who came to us with a wasted body and short of breath. He believed that he was going into acidosis from diabetes of long standing. He wasn't. In fact, he was nearly sugar free, as so often occurs in these patients. He hadn't had a physical examination in years. His dyspnoea was caused by extensive cavitation of his lungs. It became necessary to tell him. And I shall not forget the Archbishop who roomed next door and came in to one of another faith and said, "My son, may I pray with you?" They became fast friends, indeed, the Archbishop stayed on perhaps a month before the bell tolled.

It's really funny how irascible a powerful Scot can become. He had a shrewd idea of the value of life insurance and, as a result, suffered for twenty-five years from iatrogenic diabetes. I say suffered, but he really didn't diet and he knew all about the value of Scotch whiskey in treatment. He came over uninvited and how he got into the Clinic I'll never know, but he was my second case of renal glycosuria. He furnished the first chance to see if insulin would lower the blood sugar and stop the glycosuria, but fortunately, it absolutely failed in the doses used. We were very sensitive to the dangers of hypoglycaemia in those days when standardization of insulin activity was still uncertain. When I explained the situation he really laid me out. "I have spent a thousand puns on the best doctors in the wurrrld and now you — you tell me I haven't diabetes." There were eleven cases of renal glycosuria in the literature at that time.

For the first time I saw temporary diabetes. A Queen's student had several boils. Staphylococcus toxin sometimes raises the blood sugar and sometimes even glycosuria occurs, but in his case it was accompanied by ketosis. His doctor sent him up to us. He had marked glycosuria and a moderately severe acidosis. We gave him insulin. His boils healed and the acidosis disappeared. Soon, on restricted diet and insulin, the glycosuria was abolished; then insulin became unnecessary. The diet was raised gradually to normal diet, then normal diet plus glucose without glycosuria. Blood sugar tolerance tests, first with 50 then 100 grams of glucose, were normal. For years he bothered me. Whenever a life insurance man saw him, I had to recount his history. Finally he disappeared. I wish now I knew his further history. Some of these patients, I have seen one, later become permanent diabetics but it was years before I found this out.

The onset of diabetes is often insidious. Indeed, only half the diabetics have symptoms. Because of the genetic influence, a patient should test the urine of all their relations. This leads to the discovery of some cases in their early stages when most amenable to mild restriction. A more recent development is the institution of diabetic detection weeks, to discover the symptomless diabetics in the community. They do it differently in France. The Surete is alerted and whenever a gendarme sees a rather paunchy individual, "Avec une tache blanche sur les chaussures",* he packs him in a taxi and takes him to the Hotel Dieu for examination. A Paris taxi is dangerous but even so it takes the load off the feet and the feet off the beat, as was pointed out to me.

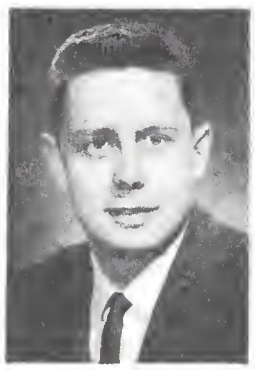
The problem of the several kinds of diabetes is not yet solved. It may startle you to learn, I know it would me, that I believe that the Cro-Magnon race has largely died out because of diabetes induced by hyperpituitarism secondary to adrenal hyperplasia caused by stress. Because of the polyuria, stress incontinence was a well known symptom. Archaelogists tell us the only remaining traces of the race are the psychiatrists and among them you will have noticed that incontinentia linguae or dribbling from their mouths, as it is phrased in the demotic tongue, is an all pervading characteristic.

The discovery of insulin is, in a very real sense, the most important foundation stone of the modern science of endocrinology and on the latter we must pin our hopes. We have wandered in the wilderness for forty years and have never come up

*An old observation perhaps lost in the maze of transaminases etc. of modern days, akin, too, with the setting out of a pannikin of the patient's urine to see if it attracted honey bees. With the welter of laboratory tests to plague us, the electronic monitoring of patients and the imminence of punch-card diagnosis, let us hope that we do not lose our capacity for clinical observation. Minkowski has related that he reproved the deaner for allowing the dog, pancreatectomized for other reasons the previous day, to soil the floor with urine and was told that it was impossible to stop it. Drawing up a small quantity, he tested it and discovered pancreatic diabetes. The which, of course, proves the value of a pipette — if nothing more.

unto Zion (There's old anabainein again—to come up unto). There has been a little manna now and then, enough to pique our curiosity but not to assuage our hunger, but slowly, surely, we shall see paradisos and enter into the land of milk and honey. This anabasis is finished but remember in Science, anabainein means to go on up and ever on. "There's *bound* to be *gold* boys, in them thar hills."

And for those of you who hope you are in no imminent danger of diabetes, here is something I wish you would do for me. Tomorrow morning when you put on your dressing gown to go in for your bath, stop briefly at the full length mirror your wife had installed in the bathroom door. I know you are modest and perhaps you won't like what you see, but do it anyway. Half the world is suffering from starvation, here is how the other half lives — and dies — *prematurely*. Now, no more euphemisms, please. You know that so-called sacro-iliac belt has done your sacro-iliacs no good and you know what would. That belt is really a corset and its sole function is to keep your belly button from flapping against your knees. I'm not your doctor, but if I were I'd make you toe the line. Huh — you can't toe the line — you can't even see your toes? I can't either.



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I-131 In the Diagnosis of Hyperthyroidism

by David MacGregor, 6T2

Introduction

Hyperthyroidism may be defined as an abnormal state due to the excessive functional activity of the thyroid gland and resulting in the release of greater than normal amounts of thyroid hormone. The condition is usually associated with enlargement of the thyroid gland, increase in the pulse rate, and sometimes changes in the appearance of the eyes characterized by undue prominence, lid spasm, and swelling of orbital tissues. Disturbances of the cardiac, gastro-intestinal, and endocrine systems are common findings in the hyperthyroid patient.[1]

Iodine was discovered as an element by Curtois in 1811. The first radioactive isotope, I-128, was prepared by Fermi in 1934. Since then radioactive iodine has become a very useful tool in the diagnosis and treatment of thyroid conditions. It is the purpose of this paper to demonstrate how I-131 may be used to diagnose hyperthyroidism. It is assumed that the reader is familiar with the basic concept of radioactive isotopes and their measurement with the Geiger-Mueller tube or scintillation counters (now in more common use).

Physiology

I-131 follows the same metabolic pathways as I-127, the normally occurring, stable isotope. Thus radioactive iodine can be used as a "tracer" because it emits energy in the form of beta and gamma rays which can be measured by appropriate instruments. Under adequate conditions the average adult ingests and excretes about 150 micrograms of iodine daily, keeping him in "iodine balance." Only iodine in the form of inorganic iodide is accepted by the thyroid gland. Most of the conversion to iodide from other forms of iodine such as elemental iodine, iodate, etc., takes place in the digestive tract. The concentration of inorganic iodide in the blood stream and body fluids is approximately 3.0 micrograms per litre. A very efficient enzymatic mechanism permits the thyroid cells to concentrate iodide from the blood and incorporate it into thyroid hormone. The level of thyroid activity is governed by a feed-back mechanism between the thyroid and the anterior pituitary gland. The iodide, trapped by the thyroid cells, is converted to iodine which reacts with tyrosine to form iodinated tyrosines. Coupling of the tyrosine nuclei produce thyronines of which the tri-iodo and tetra-iodo forms are the most important. These two forms have similar functions, but the tri-iodo form is present in much smaller quantities. The tetra-iodo form is commonly known as thyroxine. This hormone is secreted into the bloodstream where it circulates; bound to protein (PBI), normally in a concentration of 3.5 to 6.5 micrograms per 100 ml. plasma or serum. In the periphery the hormone is degraded and its iodine content is set free as inorganic iodide which in turn re-enters the body's "iodide pool." Iodine is mainly excreted in the urine, although small amounts (13%) are lost in the stool, sweat, saliva, and milk.

The normal thyroid clears about 1 litre of plasma per hour of its contained radioiodine, whereas the normal kidney will clear about 2 litres per hour. Under these circumstances about 3 litres of plasma are being cleared of iodide per hour, the thyroid receiving about one third the total dose. If, however, the thyroid clearance is increased under typical conditions of thyroid overactivity to a value of 10 litres per hour while the renal clearance remains unchanged, a total of 12 litres of plasma will be cleared of their iodide each hour. Thus the thyroid uptake would be increased from about 30% to about 80% of the dose, and this increased uptake will be achieved 4 times as rapidly.[2]

The concept of a "pool" or a theoretical volume throughout which the various iodine containing compounds are fairly uniformly distributed, simplifies an understanding of the dynamics of iodine metabolism.

The Inorganic Iodine Pool contains all the fully exchangeable iodide content of the body including the iodide in the thyroid gland which has not been converted to the protein-bound form.

The Intra-Thyroidal Hormonal Pool contains all the protein-bound iodine within the gland. This iodine is non-diffusible and with rare exceptions (eg. subacute thyroiditis), only leaves the gland under the influence of thyrotropic hormone

(TSH), from the anterior pituitary gland. The length of time for half of the stored hormone to leave the gland is known as the "biological half-life." This time is decreased in hyperthyroidism as a result of a rapid turnover of hormone. The "physical half-life" of I-131 is 8 days and the "effective half-life" represents the amount of time required for half of the radioactivity present in the gland to disappear. These three values are related as follows.[3]

$$\frac{1}{Tb} = \frac{1}{Te} - \frac{1}{Tp} \quad \text{or} \quad Tb = \frac{Tp \times Te}{Tp - Te}$$

where Te – Effective half-life
Tp – Physical half-life
Tb – Biological half-life

Effective half-life is determined by a series of measurements over the thyroid gland until the slope of the curve is adequately determined. Its value varies from less than 8 days to less than 2 days and is a measure of the amount of radiation actually delivered to the thyroid by a given amount of I-131.

The Extra-Thyroidal Hormonal Pool represents all the protein-bound iodine not contained within the thyroid gland. The concentration of hormone in this pool really determines the clinical status of the patient.

Effects on I-131 Uptake

I-131 is administered in the form of sodium iodide and can be given either orally or parenterally. Its absorption into the "inorganic iodide pool" is rapid and complete. One microcurie of "carrier-free" I-131 weighs 8.1 x 10^{-6} mg. and only a few microcuries are needed in diagnostic tests. Thus the addition of I-131 does not change the amount of iodide in the various "pools."

Iodine compounds taken by the patient can completely invalidate diagnostic studies with I-131. For instance, 1 ml. of Lugol's soln. contains 130,000 micrograms iodine, or the normal requirement for 1000 days. This tremendously increases the "iodide pool" and consequently dilutes the dose of I-131, making uptake values markedly reduced. It also tends to saturate the thyroid "trap" for iodide. Several weeks are required before the "iodide pool" returns to normal values, although this time is somewhat reduced in hyperthyroidism. If in doubt, tracer studies can be repeated at weekly intervals after discontinuation of iodide medication in order to obtain valid results.

Radio-opaque substances containing iodine such as Lipiodol are degraded and the iodide set free in unpredictable amounts for unpredictable periods of time. For example, a patient who received intramuscular Lipiodol five years previous still had marked elevation of serum PBI and markedly depressed uptake although he was clearly hyperthyroid. Large doses of iodide not only inhibit hormone synthesis but slow the release of hormone from the gland into the circulation.

Absolute iodine deficiency, as in regions where endemic goitre is common or where patients are on salt restricted diets serves to decrease the "iodine pool" and thus increase I-131 uptake values even though the patients may by hypothyroid.

Relative iodine deficiency occurs when the iodide available is either not absorbed or not utilized by the gland. Such a situation can be produced by the administration of thiocyanate or perchlorate which prevent the thyroid from trapping iodide from the plasma. Antithyroid drugs such as propylthioaracil prevent the incorporation of trapped iodide into the hormone. When these drugs are discontinued, the gland, having been depleted of hormone, will cause subsequent tracer studies to demonstrate an increased uptake of I-131 in a "rebound phenomenon."

Thyroid hormone treatment may also interfere with uptake studies. In these cases the function of the gland is suppressed and low levels of activity will be found. Thyroid preparations should be discontinued before tracer studies are attempted. For thyroid extract and thyroxine the suppression lasts for weeks or even months,[4] whereas the suppression from tri-iodothyronine lasts for a much shorter time.

ACTH and adrenal steroids may depress the uptake and increase the urinary excretion of I-131.[5]

In general, increased iodide concentrations in the "iodide pool" (low specific activity) will result in a decreased I-131 uptake, and a "pool" of high specific activity (low stable iodide concentration) will yield high uptakes even though the absolute amount of stable iodine trapped is the same in each case.

"Iodide Phase" of Iodine Metabolism

These methods of investigation study the accumulation of inorganic iodide from the plasma and its excretion by the kidney.

I-131 Uptake Studies

The ability of the thyroid gland to trap iodide enables I-131 to be used as a diagnostic tool. In general, the smallest amount of I-131 which gives dependable results in a reasonable length of time is used. This is approximately 5 microcuries, although the tracer dose varies from clinic to clinic. Within limits, the amount of tracer employed does not affect the results, but the exact dose must be known. The tracer is usually given orally, either in a sealed capsule or in a solution containing a carefully standardized dose of I-131. The time following the tracer dose at which the uptake in the thyroid is measured is usually 24 hours. The range for euthyroid, hyperthyroid, and hypothyroid subjects has been established empirically. In general, normal patients have lower uptakes than toxic subjects, but the dividing line is not always sharp. Some studies indicate that 95% accuracy in diagnosis could be obtained by uptake studies.[6] Other studies indicate that both normal and toxic states occur at almost any level except the extremes and that 24 hour uptakes exceeding 55% are highly suggestive, although not proof of hyperthyroidism.[4]

This technique measures the proportion of the "iodide pool" that is trapped and retained by the gland in 24 hours, assuming a normal "iodide pool" exists. Thus increase in the "pool" decreases uptake and vice versa. In cases of hyperthyroidism, rapid excretion of the hormone (short biological half-life) means that the peak uptake is reached before 24 hours. This results in lower readings over the gland in 24 hours than at an earlier period. Uptakes measured at 4 or 6 hours would probably eliminate this source of error.[7] One study shows that most hyperthyroid patients have uptakes in excess of 40% at 4 hours. Adams and Purves[8] suggest that uptakes taken at 8 and 48 hours yield additional information. In normals, the 48 hour uptake may exceed the 8 hour uptake by as much as 25%, whereas in hyperthyroidism the 48 hour uptake is less than the 8 hour reading. This is a result of the shorter "effective half-life" of I-131 in hyperthyroidism due to the short "biological half-life" of the intra-thyroidal hormone store. Pochin[9] points out that a further advantage of the early uptake tests is that they permit the use of short-lived radioiodines such as I-132 which are readily available in some centres. He claims that equal information can be obtained at about 1/50th the adult thyroid radiation dose in a 2 hour uptake measurement using I-132, as compared with I-131.

Age, sex, and season have only a scant effect on uptake, although it may be somewhat lower in the aged and higher in young children.

Two organs, the thyroid and the kidney, compete for the iodide simultaneously. If renal function is decreased, theoretically the thyroid would ultimately trap the entire tracer and the uptake would approach 100%. In practice, however, even in cases of severe renal failure, the uptake is only increased slightly, usually not more than 10%.[10]

Urinary Excretion Studies

Since two competing mechanisms exist, namely thyroid uptake and urinary excretion, it is apparent that they must bear a reciprocal relationship to each other. In earlier sudies this was the preferred mehod because it was easy to get exactly reproducible absolute values on a specific quantity of urine. However, errors in measuring over the thyroid do not exceed 5-10% and for clinical purposes this degree of accuracy is adequate. If urinary excretion is to be measured, the same sources of error as described earlier apply. In addition, impaired renal function or a failure to obtain an absolutely quantitative 24 hour urine specimen can produce erroneous results. Congestive heart falure, shock, and pre-renal deviation also give lowered I-131 excretions. Due to these problems most investigators prefer thyroid uptake studies to renal excretion studies. The concentration of I-131 in urine is commonly measured by the use of the "Marinelli breaker." Urinary excretions of less than 30% of the tracer dose are consistent with the diagnosis of hyperthyroidism. If the excretion exceeds 40%, the thyroid is usually normal or hypoactive (These values apply to the total 24 hour urinary excretion.) These studies are of special value where the patient is too ill to be brought to the laboratory for uptake measurements, or where the percentage of the dose retained in metastatic thyroid tumours can be estimated, provided the uptake in the normal thyroid tissue can be determined or has been abolished by previous therapy. The dose in urinary excretion studies is usually identical to that used for uptake determinations.

Thyroidal Iodide Clearance

The clearance function of an organ represents the quantity of blood completely cleared of a substance in a given unit of time. Pochin[11] found that by direct examination of the venous effluent of the thyroid in normal persons, 20% of the iodide was extracted in one passage, whereas in

hyperthyroid patients the extraction may be complete. Clearance is estimated by measurements of the I-131 uptake over the thyroid and the I-131 content of a urine sample collected over a given period of time, or by determining the average concentration of the plasma I-131. It is important that measurements be made after complete mixing of the tracer dose with the stable iodide pool and before any significant loss of the trapped iodide in the form of PBI-131 has taken place. To accomplish this the tracer dose is given intravenously and continuous measurements made over the thyroid with an automatic recording device. The test is terminated at 30 or 60 minutes. If direct measurement of plasma I-131 is employed the determination below is employed.

$$\text{Cl I-131} = \frac{\text{Thyroid I-131}}{\text{Plasma I-131}}$$

where Cl I-131 — Thyroid clearance in ml./min.

Thyroid I-131 — Total I-131 in microcuries collected by the thyroid per minute of elapsed time as determined by external counting.

Plasma I-131 — Average plasma concentration of I-131 during the elapsed time in microcuries/ml.

If the I-131 content of a urine specimen collected at the end of 30 minutes is determined, the clearance can be established by more complicated calculations.

Clearance studies are comparable to uptake studies, but are vastly superior where marked variations in renal clearance are present, or in cases where rapid uptake and release may give false values at 24 hours. However, this procedure has serious technical drawbacks, especially if a large volume of work is to be accomplished.

In normal subjects clearance values run between 0.5 and 3.5 litres per hour, whereas hyperthyroid clearance values run between 5.0 and 50.0 litres per hour.

Other Methods

Neck-Thigh Ratio. Two simultaneous symmetrical measurements over thigh and thyroid are taken 1 to 2 hours after administration of an oral tracer.[12] Ratios in excess of 7 are indicative of hyperthyroidism.

The Accumulation Gradient. Since the thyroid constantly extracts a fixed percentage of the circulating "iodide pool", the uptake can be expressed as a function of time. If counts per unit of time are plotted against the square root of the elapsed time, a straight line results, the gradient of which varies with the state of the thyroid function.[13] The slope of the straight line so plotted is termed the accumulation gradient and is reasonably constant in normal subjects. Higgins, at St. Michael's Hospital in Toronto, devised a 10 minute uptake test, which compared with other tests of thyroid function, has been found to give values in hyperthyroidism which are more significantly elevated than those for the 24 hour uptake of PBI.

Salivary I-131. The relationship between salivary I-131 to total plasma I-131, or to plasma PBI-131 is such that the salivary value is less in hyperthyroidism due to the rapid clearance of I-131 by the overactive thyroid.[14]

Salivary I-131 after oral I-131 intake[2]

	$\frac{\text{Salivary I-131}}{\text{Plasma PBI-131}}$
Hyperthyroid	0.25 — 40
Euthyroid	160 — 235
Hypothyroid	338 — 3200

Organic Binding and Release of Hormone Background

These tests are dependent upon the conversion of the trapped iodine to organically bound hormone synthesis have been dissociated such that circulation where it is bound to serum protein and therefore can be isolated from the circulating iodide. Due to the fact that these tests measure the actual amount of hormone produced and secreted into the circulation, a more accurate indication of the patient's condition can be obtained. These measurements are more likely to be consistent with clinical findings than those of the "iodide phase". In cases where anti-thyroid drugs have been employed the iodide trapping and hormone synthesis have been dissociated such that uptake studies give a false impression of the gland's ability to produce hormone.

Conversion Ratio

This is the ratio expressed as a percentage, of the PBI-131 in the plasma to the total plasma I-131 at a fixed time, usually 24 hours after the tracer dose.[16]

$$\text{Conversion Ratio} = \frac{\text{Plasma PBI-131}}{\text{Plasma total I-131}} \times 100$$

Values exceeding 50% are usually found in hyperthyroid patients. Erroneous values will be obtained if severe renal insufficiency or congestive heart failure are present, because this will allow abnormally large amounts of I-131 to be circulating at 24 hours. Also at time zero, all the I-131 is in the iodide form and the conversion ratio is zero. If one waits long enough all the measureable I-131 will be protein-bound and the conversion ratio will approach 100%. The time selected, 24 hours, usually gives dependable results but is subject to some variation.

72 Hour Plasma Levels of PBI-131

This test depends on the concentration of PBI-131, expressed as a percentage of the administered dose per litre of plasma, at about 72 hours after oral tracer administration. PBI-131 reaches a plateau with its highest levels appearing between 48 and 96 hours, so that the time of taking the blood levels is not critical. Also, since I-131 levels are not considered, factors such as renal insufficiency and congestive heart failure will not alter the results. In normals the PBI-131 level does not exceed 0.27% of the administered dose per litre of plasma at 72 hours. In hyperthyroidism the value is usually between 0.42 and 5.60% of the administered dose per litre of plasma.[17] However, in cases of severe albuminuria, the level of PBI-131 may be markedly decreased due to urinary loss of same.

For both of the above methods 25 microcuries of tracer are given orally. In the conversion ratio the exact dose is not critical because only ratios are being considered. In the 72 hour PBI-131 test the exact dose must be known. For the PBI-131, venous blood is drawn at 72 hours and the total plasma I-131 is determined by a well-type scintillation counter. If the concentration exceeds 0.27%, then the inorganic I-131 is removed by "washing out" techniques or by an ion-exchange resin, and if the remaining concentration of I-131 as PBI-131 exceeds 0.27% of the administered dose per litre of plasma then the patient is in the hyperthyroid range. These tests are invalid if drugs which interfere with the trapping or organic binding of iodides have been used. These include thyroid hormones, anti-thyroid drugs, large amounts of iodine, amphenone, cobalt, phenylbutazone para-amino-salicylic acid, resorcinol, plus the newer oral anti-diabetic compounds, tolbutamide and carbutamide.

In Vitro Use of I-131 Labeled Tri-iodothyronine

This technique depends upon the incorporation of I-131 labeled tri-iodothyronine by erythrocytes.[18] Red cells from hyperthyroid patients show a higher fixation of labeled hormone than red cells from normal or hypothyroid patients. Walfish et al., in Toronto,[19] have studied the R.C.U. test (the red cell uptake test, i.e. the calculated percentage uptake by the red cells of L-tri-iodothyronine labeled with radioactive iodine). They point out that the chief advantages of the R.C.U. test over the other tests of thyroid function are that it is not significantly influenced by iodine contamination; it avoids the administration of radioactivity to the patient; and it provides another aspect of thyroid physiology by measuring the ability of certain unsaturated plasma proteins to bind added I-131 labeled tri-iodothyronine.

Other methods which aid in the diagnosis of hyperthyroidism at a research level include the Thyroid Secretion Rate[20], the Thyroxin Degradation Rate[21], and Chromatography[22].

Assessment of Methods

The two most commonly employed diagnostic procedures are the uptake of I-131 by the thyroid gland, measured 24 hours after the oral administration of the tracer dose, and the measurement of the concentration of PBI-131 in the plasma 72 hours after giving the oral tracer.

In general, uptake studies are not as accurate a diagnostic test as the levels of PBI-131 at 72 hours after the tracer dose. In a series published by Silver et al.[4] it was found that if a critical value for the PBI-131 of 0.27% of the administered dose per litre of plasma is taken, there were 1.6% errors in classification. At a critical 24 hour thyroidal I-131 uptake value of 61% there were 7.2% errors in classification. To reduce the diagnostic error of the uptake method to that attained by the determination of PBI-131 it is necessary to select a critical range of an uptake between 42% and 69% as "unclassified." However, this range theoretically leaves about 25% of the cases unclassified, whereas the PBI-131 method attains the same accuracy with no unclassified cases.

One must also be careful not to attribute undue faith in I-131 as a diagnostic procedure. The clinician must only use these tests in conjunction with a thorough history and physical examination, and other diagnostic procedures such as the serum

protein-bound iodine level. It is on the basis of a critical examination of all this data, that a correct diagnosis is made. This is particularly true in patients who have received drugs which affect I-131 studies, who have depleted iodide pool, or who have severe renal insufficiency or congestive heart failure. One should not treat a patient for thyrotoxicosis purely on the basis of I-131 studies. Awareness of these "false hyperthyroid results" with I-131 testing will prevent the unnecessary treatment of normal subjects, and prevent the further treatment of persons who have been cured of thyrotoxicosis, with the possibility of resulting myxoedema.

"The Pythia of the oracle that we consult may be electronically operated, but she remains at heart very much an oracle."

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UPJOHN ABSTRACT: *Therapeutic Trends in the Treatment of Barbiturate Poisoning; The Scandinavian Method;* Clemmesen, Carl; Nilsson, Eric; Clin. Pharmacol. Therap. 2:220-229 (March-April) 1961.

The mortality rate in patients with barbiturate poisoning has been reduced since the introduction of the "Scandinavian method" of treatment, i.e., since elimination of central analeptics from the treatment and rigidly observing physiologic principles in therapy, antishock measures, a free airway, and possibly the use of oxygen. This regimen requires intensive treatment until the unconscious patient is out of danger. With its use, the mortality rate has been reduced to 1 or 2%, whereas the rate was previously 20% despite utilization of intensive central stimulation.

The Scandinavian routine in detail includes attention to the cardiovascular system, corticosteroids and the circulation, respiration and the airway, the place of bemegride, artificial ventilation, renal complications, and alkalinization and forced diuresis.

Investigation of Infertility

by M. L. Waite 6T2

For many centuries, the age-old problem of the barren marriage has engaged the interest of the physician. This is more than merely a medical problem because the welfare of society, and the stability and happiness of the marital union is involved. The physician who undertakes to deal adequately with this problem must learn to understand and treat the whole person, indeed, the "whole" couple. "This universal interest in human fertility as well as having permeated the general mores, has became a part of many religions. Societies that otherwise insist upon a monogamous and lasting marriage will, if the marriage proves infertile, permit second wives, concubines, divorce, or adoption. In the United States refusal to procreate can be grounds for annulment." When it has been estimated that one in seven marriages prove to be sterile, the magnitude of this problem can be appreciated.

This paper will not deal fully with all aspects of investigation, but will suggest an outline for the programme of study of a sterile couple. More detail will be given concerning the investigation of the male partner, and some of the newer concepts concerning the role of spermatozoa will be discussed.

Sterility is considered primary when conception has not occurred after the lapse of one or more years of continuous marital life without the use of any contraceptive measure. It is termed secondary when one or more pregnancies are followed by one year of involuntary barrenness. Since the etiology is identical no distinction will be made in the following discussion.

The first question encountered in this problem concerns the time that proper investigation should be started. It is the fate of many couples when they seek advice to be merely given encouragement and told to return in six months. At the end of this interval the same advice is again offered. This attitude on the part of a physician is to be deplored, when reasonably accurate diagnostic aids and investigational measures are readily available. It is true that there are a number of cases in which no abnormality will be found, but this is no reason to neglect systematic investigation. A few of the more skilled studies require the help of a specialist, but much of the investigation can be done by the family physician. The following figures may aid the physician in determining the best time to begin fertility studies. After many surveys it is estimated that 90% of couples eventually conceive; 59% do so at the end of 6 months' trial; 73% have success in one year; 82% by 2 years; and 8% succeed only after more than 2 years of trial. Since couples with six months of conception failure do have an increased chance of falling into the sterile group, it is legitimate to evaluate reproduction function at this time. Southam outlines the following plan of investigation. At six months, history, physical examination and simple screening procedures such as the postcoital test or basal body temperature pattern will identify many of the probable sterile couples. Further diagnostic procedures are not indicated unless suggestive factors are found. At the end of one year, the criteria for normality must include proof of tubal patency, ovulation, normal endometrial histology, normal semen qualities and adequate insemination. If these factors are normal and if history and physical examination are unrevealing, continued optimism is justified. The probability of sterility ensuing after two years of unproductive endeavour is 54%. A carefully executed and interpreted hysterosalpingogram is indicated at this time and the study should include a 24-hour film. By the end of the fourth year, duration of infertility becomes a serious prognostic factor especially when the woman is approaching 35 years of age. Diagnostic surgery, either culdoscopy or exploratory laparotomy seems justified to rule out such occult abnormalities as peritubal adhesions or endometriosis. One author has reported a decrease of 34% by using these procedures at this time.

Factors in infertility

Let us now consider the five major factors involved in infertility: grossly recognizable pelvic conditions, insemination of the cervix, the tubal factor, the endocrine factors, and the male factor.

Grossly recognizable pelvic conditions.

Approximately 5% of women are found to have uterine leiomyoma, endometriosis, ovarian tumor, chronic pelvic inflammatory disease, significant malpositions and congenital malformations of the

uterus. The relative importance of leiomyoma may be determined by their size, number and location. Such tumors are important if they cause either tubal or cervical obstruction or if they are submucous. Endometriosis may cause tubal occlusion and ovarian dysfunction. Unfortunately, only one of four patients with endometriosis have palpable abnormalities. Malpositions of the uterus are frequently implicated but infrequently proved to be detrimental to conception. Only rarely does the anterior position of the cervix encountered in retroversion of the uterus interfere with the entrance of spermatozoa into the cervical canal.

Insemination of the cervix.

This topic includes failure to deposit the semen in the vicinity of the external cervical os, inadequate invasion of the cervical canal by spermatozoa properly deposited, hostility of both vagina and cervical secretions, and failure of spermotozoa to ascend above the internal os. These factors are evaluated by means of the Sims-Huhner or post-coital examination of cervical secretions. The post-coital test is most valuable when examination is made 6-8 hours following intercourse; when cervical mucous is favorable, i.e. at ovulation, and when the test is preceded by a few days of continence.

This test was used at Washington University for the investigation of lethal factors in the vagina and cervix. Family units were studied in whom no abnormalities were found in either partner but who had a persistent negative post-coital test. Immediate post-coital tests were made after a period of vaginal control study for one week. Intravaginal contents were removed every 15 sec. for 1 minute then at minute intervals 5 times and finally at 10 minutes. If the test was negative, in vitro studies were made with semen and cervical mucous at ovulation. In some cases, the cervical mucous did not inhibit the sperm and the vagina provided the lethal environment. In other cases the cervical mucous was responsible. Both male and female exchanges were made before conclusions were drawn. Of 17 families, 15 had lethal factors in the vagina, and 2 in the cervical mucous. Various combinations of blood groups were used to discredit previous claims that blood group incompatability was responsible. As a practical point, when the Sims-Huhner test shows no sperm in the cervical mucous the lethal factor is probably in the vagina, and when it shows immobilized sperm, the lethal factor is probably in the cervical mucous. These studies in cases of infertility are important because methods are now being devised to inseminate the female and by-passing these environmental abnormalities.

The tubal factor.

Partial or complete occlusion of the Fallopian tubes may be demonstrated by means of transuterine insufflation of carbon dioxide (the Rubin test) or hysterosalpingography. Partial obstruction may result either from actual constriction or a state of disturbed function. Some feel that the Rubin test is also of therapeutic value for partially occluded tubes, as a higher rate of conception has followed the test than would normally be expected. In the absence of acute or chronic pelvic disease including Trichomonas vaginalis, or uterine bleeding, the test may be safely performed in the physician's office between the fourth and seventh day following cessation of a normal menstrual period. The test will indicate patency and peristaltic movements of the tubes, but does not indicate which tube is patent. An erroneous result may be obtained when spasm of the tubes is present. A diagnosis of occlusion is not made unless three negative tests are obtained, as outlined by Rubin. The apparatus must be free from mechanical difficulties and technical errors avoided in order to obtain accurate results. A hysterosalpingogram is indicated when the Rubin test shows abnormalities, or after a further period of time without conception following a normal Rubin test. Occasionally a hystersalpingogram may show one tube blocked when the Rubin test is normal.

The endocrine factors.

A complete investigation of the endocrine factors is not available since accurate knowledge of the many involved endocrine relationships has not as yet been obtained. Three main groups of endocrine factors should be studied: abnormalities of menstrual rhythm, namely amenorrhea and dysfunctional metrorrhagia, anovular menstruation, and inadequate progestational preparation of the endometrium. A discussion of these factors including pituitary and hypothalamic, thyroid, and adrenal hormones is not attempted at this time. Fascinating research, including that of the delta cell of the pituitary gland in which Dr. C. Ezrin of the Toronto General Hospital is engaged, is being carried on and more hormonal relationships are constantly being outlined.

One of the most basic studies of the hormonal factors in fertility is the determination of ovulation. The fact that numerous tests have been

devised for this purpose indicates that no one test is completely accurate. The most universally employed method for detecting ovulation is the basal body temperature chart. Ovulation is thought to occur either at the low point before the sustained rise, a day or two before this point, or on the rise from low to high. Sometimes the graph may be difficult to interpret. A more accurate method of determining ovulation is the use of vaginal smears. The smear shows increasing evidence of oestrogen with the appearance of cornification at midcycle. Following this the cells become clumped and exfoliated. The smear cannot be used in the presence of vaginitis and cervicitis, and may be difficult to interpret following coitus. Its use is further limited because of the need of cytologic training.

Another useful test is the observation of the cervical mucous, noting the threadiness or spinnbarkeit. The mucous can be "stretched" to increasing lengths until the time of ovulation, when it becomes thick and scanty. Some feel that maximal spinnbarkeit is the best indication of optimal fertility. The fern test is used by some investigators. Around the time of ovulation, when the cervical mucous is allowed to dry it shows crystallization or ferning. However, this phenomenon may last a few days, and in such cases the usefulness of the test is limited. Newer methods for ovulation determination are constantly being devised. The Glucose Stick Test and the Fertility Testor (a modified glucose indicator) have not found widespread acceptance due to their unreliability. Any of these methods may be used with patients complaining of infertility.

A woman may have an adequate follicular phase producing sufficient oestrogen to set off the ovulatory mechanism without the subsequent presence of an adequate corpus luteum. Fertilization may occur, followed by silent abortion, masquerading as sterility. Premenstrual curettings show inadequate glandular development associated with patches of dense stroma. If available, pregnanediol assays show premature disappearance from the urine, indicating insufficient progesterone levels. The basal temperature chart shows a failure to maintain the increase of temperature that occurs after ovulation.

The male factor.

Until recently, the blame for infertility has solely rested on the woman. In the last 50 to 100 years, man has slowly been descending from his lofty perch of fertile perfection, and, even though reluctantly, he is assuming his rightful position in the problem of infertility. Presently, it is calculated that the male is partially or wholly responsible in about 40% of infertile couples.

The most basic investigation apart from history and physical examination is semen analysis. There has been considerable disagreement about what constitutes normal semen, but the following criteria is usually accepted. On 3 different occasions, the following factors are noted:

Volume. 2.5 c.c. is considered too little and 6.0 c.c. too much. Rubin has made some interesting observations about the importance of volume. Studies from insemination procedures show that in cases with a small volume of less than 1.6 ml. with a high sperm count 75% conceived, whereas in cases with a large volume and low sperm concentration had success in 46%. In his series, a small volume occurred in 7% of patients and a large volume in 13%.

Viscosity. Watery semen usually suggests other abnormal seminal factors. Markedly viscid specimens immobilize spermatozoa.

pH. It must be alkaline.

Count. Until recently the lower limit of normal was considered to be 60 million/c.c. With further investigation, the limit has been set at 20 million.

Morphology. Usually 15-30% abnormal forms are permissible, but there is a great difference of opinion on this subject.

Motility. In the presence of a normal sperm count, immotile, normally-constructed spermatozoa are just as worthless as vigorously active strange-looking abnormal organisms. The character of the motility and the number of motile sperm compared to a time factor since ejaculation should be noted. At 4 hours, 60% should have rapid movement.

Wet and Gram stain smears are made to look for purulent material and bacteria. It is known that infection has lethal properties.

This criteria cannot be used absolutely, because there may be more than one factor present.

There are many known, some theoretical and unknown causes of azoospermia, oligospermia and necrospermia. Only passing mention can be made of faulty spermatogenesis due to endocrine disorders of all types, abnormal germ plasm seen in Klinefelter's syndrome and spermatogenic arrest, nutritional factors, and environmental factors such

as high temperature as seen in cryptorchism, varicocoele, hydrocoele, faulty circulation, inflammation, exposure to radiation and trauma.

There are, however, other factors currently being investigated which can cause abnormalities of semen. One of these is the role of seminal plasma in the motility of spermatozoa. Recent work has shown that seminal plasma of normal human semen stimulates the motility of sperms of low motility from oligospermic semen. The seminal plasma of oligospermic semen with spermatozoa of low motility decreases the motility of normal semen with spermatozoa of good motility. These experiments have shown that seminal plasma has an important function in the maintenance of motility of spermatozoa. Comparison of reducing sugar and lactic acid contents of normal semen and of semen with azoospermia indicates that when the spermatozoa come in contact with secretions of certain accessory glands of reproduction, prior to ejaculation, glycolysis is initiated. The high buffering capacity of the seminal plasma protects the spermatozoa against the low pH of the vaginal secretions and the high fructose content of the seminal vesicle component of the seminal plasma supplies the spermatozoa with a readily utilizable substrate until they are able to reach the more hospitable environment of the cervical canal. In view of the relatively high incidence of disease of the male accessory glands of reproduction without involvment of the testes, it is evident that the pathology in many subfertile or sterile semen specimens may be due to the harmful effect of abnormal seminal plasma on normal spermatozoa.

Another factor of current interest is the contribution of autoimmunity to the problem of infertility. It has been known since 1900 that sperm injected into an animal produces an antibody response. Cross reactions showed that mammalian sperm possessed both species and tissue specificity. In guinea pigs aspermatogenesis, anaphylaxis and cutaneous sensitization occurred from homologous testicular extract. There is a double nature of spermatozoal antigenicity. One antigen is of original endowment and is seen in sperm taken from spermotocoeles. The main antigenic properties, however, are acquired from the seminal plasma. This antigen is taken up by the sperm and firmly adheres to it. Interest in antibody formation began in 1954 when Wilson observed that blood sera of 2 men whose sperms spontaneously agglutinated contatined agglutinins for sperm. Three types of agglutination have been observed: head to head, tail to tail, and mixed. The type of agglutination in semen is similar to the type observed when normal sperm is added to the serum of the patient. Biopsies show that the agglutinins do not affect spermatogenic tissue. This phenomenon is often associated with occlusion of the efferent ducts, and it is therefore thought that spermatozoa may induce autoantibody formation when they are in contact with the circulation. In examination of 2015 "sterile men", it was found that 3% had sperm agglutinin titres of 1:32 or higher. In examination of sera, there is equal distribution of infertile females and males with positive agglutination. Agglutinins have not been detected in patients with no history of infertility or in unmarried females. Much investigation is being carried out, with respect to aetiology of infertility and also vaccine formation to cause sterility.

Another diagnostic aid that is being used more frequently and with increasing value is testicular biopsy. Normal tissue shows adult maturity at the age from 13-16. The age of decline varies from 50 to 70, and is manifested by a decreased number of functioning tubules, sclerosis, peritubular fibrosis and premature sloughing of spermatogenic epithelium. Because of the recent inclusion of biopsy in diagnostic helps, normal variation patterns are still being delineated, pathological criteria is being standardized, and technique is being perfected. Biopsy is not recommended as a routine procedure, but is most useful in cases of azoospermia, endocrine disorders and severe oligospermia. A normal test pattern in patients with azoospermia proves mechanical obstruction. Some of these mechanical factors are amenable to surgical procedures such as epididymovasotomy, varicocoelectomy, and correction of cryptorchism. Probably in the future, testicular biopsy will have more widespread use in fertility problems.

I would like to mention one other area of research in the investigation of infertility. Weir and Leuchtenberger made a study of 35 infertile couples with no demonstrable abnormalities and 25 fertile couples. In all cases the semen analysis was normal. In serial specimens, the DNA content of the spermatozoa was measured. All values in the fertile couples were normal. In the infertile group only 2 of 35 had normal DNA in all specimens. In the infertile group DNA value was normal in 14.9% of 148 specimens and in the fertile group, the DNA value was normal in 100% of 114 specimens. Of the 35 infertile couples, 2/3

eventually became pregnant with a 26% abortion rate.

At present, much of this investigation is being conducted at research levels and is not available for routine use. This material was presented merely to show the trend of scientific investigation and future possibilities in evaluating the male partner.

Summary

Although no attempt has been made to adequately cover the topic of investigation of infertility, a brief outline has been presented that will enable the physician to systematically investigate his patients. It was suggested that infertility studies begin at six months with more definitive tests to be used at later periods. The major factors involved with their respective investigation were discussed under the headings: grossly recognizable pelvic conditions, insemination of the cervix, the tubal factor, the endocrine factors, and the male factor. Some of the recent developments in the investigation of spermatozoa were outlined.

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ABSTRACT: *Massive Niacin Treatment in Schizophrenia;* Osmond and Hoffer; The Lancet, 10 February, 1962, pp. 316-319.

The authors present the results of a nine year study of the treatment of schizophrenia with niacin or nicotinamide. An initial small double-blind study of 30 patients in 1951 indicated that these drugs might be beneficial. Of 73 patients treated for schizophrenia with niacin from 1952 to 1955 28% had been readmitted by 1959, as opposed to 57% of 98 patients who received other treatment. A second double-blind study of 82 patients showed the best results were obtained when patients received niacin for a long time after discharge as well as while in hospital. Of the 62 patients who received niacin, 55% were well after five years ("five year cure"), as opposed to 20% of the 20 patients who had other treatments.

The rationale for using niacin in schizophrenia relates to the adrenalin metabolite theory. The authors have worked on the specific idea that adrenochrome, a derivative of adrenalin, is the causative factor in schizophrenia. If niacin were used, it would theoretically compete for methyl groups and so prevent more noradrenaline being methylated to adrenalin.

The suggested treatment with niacin or niacinamide is 3 to 6 grams every day for three months combined with any other treatment thought necessary. If improvement is noted, it should be continued for a year; if not, the patient may be admitted to hospital and treated with sedatives, tranquillizers, and later a course of 8 to 20 electro convulsive treatments in addition to the niacin.

This empirical remedy, although seemingly ineffective in chronic cases seems to induce a degree of protection against schizophrenia. The authors hope that the advantages of niacin will be recognized, and that a large scale test can be arranged in the near future. J.D.G.

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The Comatose Patient

by Jack Shuber 6T3

In recent years, the field of coma, its aetiology, physiology, diagnosis, and therapy has become more and more interesting. With each year more papers appear to clarify the problem, its mechanism, and management. The texts become more vague and students often go through most of their undergraduate training without really understanding the problem. It is the hope of this paper to provide a concise, workable, and it is hoped, a complete review of the theories and methods presently applied to the state.

Background

Neurophysiology

For many years the mechanism of maintenance of the conscious state and its exact nature have been buried in obscurity. More recent work has done much to clarify our knowledge on the subject.

The states of attention, consciousness, and sleep depend upon a common physiological mechanism. This mechanism is maintained by the central reticular formation of the brain stem, in the floor or tegmentum of the fourth ventricle, in the medulla, pons, and mid-brain. This area is a web-like reticulum of nerve fibres with nerve nuclei embedded in it. These nuclei receive afferent fibres from tracts below and nuclei within the formation. They, in turn, send impulses to parts of the hypothalamus, subthalamus, and thalamus via the ARAS (ascending reticular activating system). Another system, the DTPS (diffuse thalamocortical projection system), transmits impulses from non-specific thalamic nuclei to the cortex.

It is this mechanism, using stimuli which the body is constantly receiving, which maintains the brain of the conscious state.

Pathological Mechanism

When this mechanism of the central reticular formation is upset, altered, or destroyed, by any means, consciousness is impaired and various stages of "unconsciousness" occur. These are a series ranging from confusion, through stupor, semi-coma, to coma.

Generally the problem is due to the breakdown in the inter-neuronal relations in the formation. This may be direct damage to the formation in any part, or a form of indirect damage. Direct damage may include haemorrhage, decreased blood supply, pressure, or trauma. Indirect damage includes discharging lesions such as epilepsy, alterations in blood constituents, uremia, hepatic damage, anemia, or respiratory insufficiency.

Definition

Coma may be defined as "a state of complete, or almost complete, loss of consciousness from which the patient cannot be aroused by ordinary stimuli, sometimes not by even the most painful or powerful stimuli. It is a state of complete unresponsiveness to the environment."[2]

This definition has been clarified in recent years to avoid confusion. Thus semi-coma would include such cases where the use of painful, powerful stimuli produce arousal, however brief or stuporous. Coma would be confined to cases where arousal, even by these means, is impossible.

Signs

In true coma then, there are no voluntary movements, action being limited to reflexes which maintain the living state, viz. respiration, circulation, and gastro-intestinal activity. Others, such as corneal reflexes or sensation, swallowing or coughing, reaction to painful stimuli (pressure on the eyeballs or rolling the supra-orbital nerve), sphincter tone, cutaneous and deep reflexes, are absent to a greater or lesser extent. In very profound coma, the deep reflexes may be exaggerated and the Babinski response may be present.

Lindsley has differentiated coma from other states such as sleep, by the following criteria:[5]

EEG shows isoelectric to irregular large slow waves. The normal pattern of wakefulness shows the integration of two frequency ranges; the alpha rhythm, eight to fifteen waves per second and the beta rhythm, sixteen to twenty-five waves per second. In deep sleep and light coma the waves become the large, slow, irregular, two to three per second type.

State of Awareness. There is complete loss of consciousness, little or no response to stimulation and amnesia.

Behavioural Efficiency is absent.

In Emergency

It is recognized that in certain cases of coma before diagnosis should be attempted, certain more basic procedures to maintain life may be in order.

Emergency Examination

At this stage this should be a very brief appraisal of the patient, to include state of respiration, air entry, presence or absence of shock, haemorrhage, and fracture, especially of skull or cervical vertebrae.

With this in mind one should note the patient's colour, skin temperature, presence or absence of sweating, haemorrhage, incontinence, both fecal and urinary, rate and force of respiration, blood pressure and peripheral pulses.

This should be followed by a rough appraisal of the state of consciousness. Raise the lids and check the pupillary response, do a corneal reflex, roll the supra-orbital nerve or pinch the tendon achilles.

The examination is completed by checking for nuchal rigidity, palpating the abdomen and costo-vertebral angle, and surveying the state of the skull, long bones and ribs.

In this way any problems demanding immediate attention will be uncovered and can be attended to.

Emergency Measures

The three primary states requiring immediate attention are asphyxia, haemorrhage, and shock.

Asphyxia. This may be apparent on preliminary examination or may be feared in the immediate future. The patient is placed on his side in the semi-prone position or in the prone position with his head turned to one side. Nasal and oral secretions blood, vomitus, or any obstructions including the tongue, will tend to flow or fall down and out thus maintaining the airway patent. The attendant should check for any obstructions and attempt to clear them. Mucus and blood should be sucked out as far down the respiratory tree as is feasible. If danger of the mouth closing exists, an oropharyngeal tube may be inserted to maintain the airway.

In certain cases, such as persistent partial obstruction or abnormal respiratory mechanisms (paralysis, toxins, poisonous gases) artificial respiration or oxygen therapy should be instituted. If no emergency equipment is available do not hesitate to use mouth-to-mouth respiration. With oxygen available, any method (tent, mask, catheter) may be used, always ensuring that the method is being effectively applied.

Haemorrhage. The application of direct pressure and its maintenance over the bleeding site is the best method to stop haemorrhage. Once controlled other measures such as pressure bandages or hemostatic clamps might be attempted to maintain control.

Shock. The shock in coma may have been initiated in several ways. An absolute decline in blood volume may occur due to haemmorhage, loss of fluid or whole blood into injured tissues as in trauma or burns. In addition, this may be due to a deficit in extracellular fluid volume brought about by a decreased intake or excessive loss of water and electrolyte. A relative decline in blood volume may occur; the shock being due, in part, to loss of vascular tone, as might occur with cord transection.

Thus in the comatose patient the clinical signs of shock should be very closely checked for. These include:

cold, clammy skin
collapsed peripheral veins
increased, thready pulse rate
palor and cyanosis of the mucous membrane
restlessness (not applicable when in coma)
falling blood pressure
decreasing pulse pressure
anorexia and nausea (not applicable in coma)
diminished urinary output.

The use of external warmth, recumbent semi-prone position with the head lowered ten to fifteen degrees below horizontal, intravenous fluids in the form of blood or plasma, and oxygen should be familiar to most. Blood for typing and crossing should be taken as soon as possible. The needle used should be left in place in the event that if shock develops, a means for transfusion is available even though venous collapse may have occurred. While this is being done plasma expanders and saline may be used to restore volume but only as a temporary measure until the proper medium is decided upon.[8]

Aetiology of Coma

With the danger of impending death removed for the present, it is now the time to determine

the causative factor of the coma and institute its therapy.

The Causes of Coma Presenting in Hospital

The aetiology of coma encompasses almost the entire field of medicine, coma being due to a large number of conditions and being the terminal stage of almost any disease.

In 1934 at Boston City Hospital, 3% of all admissions presented in coma.[12] This represented 1167 cases of 37,438. Of these the following classification was made.

Problem	Admissions (%)
alcoholism	59.1
trauma	13.0
C.V.A.	10.1
poisoning	2.8
epilepsy	2.4
diabetes	1.7
meningitis	1.7
pneumonia	1.7
congestive heart failure	1.4
exsanguination	under 1
CNS lues	under 1
uremia	under 1
eclampsia	under 1
miscellaneous	3.2

Many cases of trauma were associated with the use of alcohol such that 62% of admissions had alcohol as a primary or secondary cause.

It is interesting to note that although medicine has made great strides since 1934, the etiology of coma cases has no changed to any great extent. Verbal communication here in Toronto with physicians at the major city hospitals outlined a similar relationship between the four larger groups, viz. alcoholism, trauma, cerebral vascular disease, and poisoning.

Although accuracy of diagnosis may be only 50% as was shown by Holcomb[4], still these areas remain the major areas of causation and therefore should be uppermost in our minds at diagnosis.

The classification of coma is a very large and unwieldy one and to this end various authors have attempted to work out a method of simplification. Mount attempted a classification involving two large groups: a) brain primarily involved b) brain primarily not involved.[9]

Some Toronto clinicians make use of a valuable vowel classification;

A — anoxia, general or local
E — epilepsy or other discharging lesions
I — injury or insulin
O — opiates and other poisons
U — uremia and any other metabolic problems

Within each of these areas are included a large number of similar or related factors.

Adams has found that the demonstration of certain signs has produced a valuable approach to a more clinical form of classification.[3] The use of focal or lateralizing neurological signs, cellular content of cerebrospinal fluid and signs of meningeal irritation have produced a classification which allows more rapid clinical evaluation and diagnosis. If one is fortunate enough to have these signs present the diagnosis may be simplified. However, too often they are absent.

It is therefore necessary to have in one's mind a complete classification to turn to. Meyers and Meyers have suggested the use of the mnemonic device COMA-PIC (coma picture).[7] It is useful for two reasons. First it includes a very broad classification and secondly it allows for ready recall in an emergency.

PARKE-DAVIS MEDICAL WRITING PRIZE

The editorial staff of the University of Toronto Medical Journal takes pleasure in announcing a new prize for undergraduates, who contribute to this Journal. The conditions follow:

1. The prize shall consist of $300.00 and a plaque awarded annually in the month of April.
2. All undergraduates enrolled in the University of Toronto Faculty of Medicine shall be eligible for this prize with the exception of the Editor-in-Chief of the University of Toronto Medical Journal.
3. A committee of professors and teaching staff of the Faculty of Medicine shall make a yearly recommendation to the Parke-Davis Company, as to who the winner for that academic session shall be.
4. The prize shall be awarded to the student who, in the opinion of the selection committee, has contributed to the University of Toronto Medical Journal, the article that combines the best use of the English language with the best effort in preparation. Evidence of careful examination of the medical literature about the topic selected by the student shall be an important criterion. Reports of research conducted by the student himself will be acceptable and favourably considered.

C — cerebral factors
O — opium and other drugs, chemicals, metallic toxins
M — metabolic factors
A — anaemia factors
P — psychogenic factors
I — infectious factors
C — cardiovascular factors

Cerebral Factors

Trauma
Vascular "Accident,
a) thrombosis
b) haemorrhage
c) embolism
Tumour of Bone, Brain, Meninges or vessels
Infection
a) pyogenic
b) virus
c) tuberculosis
d) luetic
e) other parasites and infestations
Malformations
Postconvulsive stupor

Opium and Other Drugs

Alcohol
Antihistaminics
Carbon Monoxide
Phosphorus
Salicylates
Others of less importance or frequency would include the opiates and other narcotics, industrial toxins, and drug overdoses.

Metabolic Factors

Alkalosis
Addison's Disease
Cholemia
Dehydration
Diabetes mellitus
Hypoglycemia
Hypothyroidism
Heat exhaustion
Sunstroke
Toxemias of pregnancy
Uremia

Anemia Factors

Haemorrhage (manifest and/or occult)
Hyper- Hypo- and aplastic anaemias
Leukemias

Psychogenic Factors

Malingering
Psychoneurosis (hysteria)
Psychosis (catatonia- acute depression)

Infectious Factors

Dysentery
Influenza
Pneumonia
Tetanus
Typhoid Fever
Exanthemata
a. Diphtheria
b. Measles
c. Scarlet Fever
d. Smallpox

Cardiovascular Factors

Adams-Stokes' Syndrome
Cardiac Arrest
Coronary Occlusion
Hypersensitive Carotid Sinus
Hypertensive Encephalopathy
Syncope

Differential Diagnosis

A careful history from a witness or a relative of the patient is a valuable factor at this time. However all too often such a history is not available and the physical examination and laboratory tests become all important.

It is not the place of this paper to go into the diagnosis of every condition which might produce coma. However, a brief appraisal of the most frequent causes might be in order.

Alcoholism

The diagnosis may be suggested here by the flushed face, the odour of alcohol, perhaps a history of drinking or benders. The frequency with which alcohol is linked to trauma or infection or malnutrition is so great that a true diagnosis can only be made on the exclusion of all other causes. Most cases of alcoholic coma are neither deep nor prolonged. Rarely, may you get a case so profound as to show loss of pupillary or corneal reflexes. Such a case may be fatal and the use of respiratory stimulants and the treatment of shock may become essential.

Trauma

As has been pointed out trauma of various kinds may occur producing haemmorhage, shock, perhaps coma. Manifest haemmorhage and shock will be readily diagnosed and treated.

Brain trauma plays a large part in traumatic coma. Concussion may be the cause, this form of coma being usually quite short, but not necessarily so. Contusion and laceration coma is abrupt

in onset and continuous from the time of injury on. With epidural or subdural haemmorhage there is most often a lucid interval after the injury, especially if combined with concussion or contusion.

Diagnosis will depend on the history of trauma, a bruised scalp, a skull fracture, or blood in the cerebrospinal fluid. With no history a skull X-ray and a lumbar puncture should always be done. The presence of positive neurological signs in a coma case point to at least some major intracranial problem. Thus inequality of pupils, conjugate deviation of the eyes, asymmetry of facial movements, spasticity or flaccidity of limbs, altered deep or superficial reflexes from one side to the other, ankle clonus, signs of an upper motor neuron lesion, all these should be sought with great care during the physical examination.

Cerebrovascular Disease

Spontaneous subarachnoid and intracerebral haemmorhage are the most common causes of coma in this area. In almost all cases the unilateral paralysis can be detected, even in coma, by the still, motionless, flaccid arm and leg. The coma is progressive over a few hours and is deep. Infarction due to embolic or thrombotic phenomena causes severe coma less often than haemmorhage.

Poisoning

The number of possible aetiologic factors in this area may be overwhelming. A history of the use of sleeping tablets, the finding of an empty pill bottle or pill box may be helpful. Very few of these agents produce a truly pathognomonic picture.

Examination to exclude all other causes is essential. Hints to the causative agent may be found in the patient's colour, for example in carbon monoxide poisoning the cherry red mucous membrane with the mottled, pallid skin. The odour of the patient's breath may give a clue. The state of pupillary contraction may also help:

mydriasis — belladonna or a derivative
miosis — opium derivative
mid-dilation — barbiturate

The many other forms of poisoning will be diagnosed by the use of history, examination, laboratory techniques, and the particular physician's or student's experience and acumen.

In any case of coma, findings on history and physical will be the guide to any further laboratory work.

Conservative Measures

These measures are a general group which may be used while the patient is under investigation as well as during therapy.

Diagnostic and therapeutic Measures

The pulse rate, blood pressure, respiratory rate, and rectal temperature should be taken at twenty minute intervals at first. Then, as the case progresses, the frequency will be altered depending on the tendency of these vital signs to change.

The patient should be catheterized. With a great deal of distension and retention, decompression should be accomplished slowly. A sample of urine is sent for urinalysis.

Blood work should be done and sufficient should be withdrawn to do all the necessary tests including culture.

Diagnostic lumbar puncture may be done unless definitely contraindicated.

Stool specimen should be taken and tested for blood and parasites. When necessary culture should be done.

Prophylactic antibiotic therapy may be necessary in some cases.

General Care Measures

Skin. The patient should be placed on a roller mattress or pillow props. If these are not available care should be taken to ensure that the patient is turned every two hours. This will prevent the production of decubitus ulcers (bed sores) at the pressure points. Sheets should be absolutely tight with no wrinkles. They must never be allowed to remain damp. Any ulcers that do develop should be treated immediately. Any red areas should be treated vigorously with massage, pads or rings, and tincture of benzoin to toughen them and thus prevent breakdown.

Temperature. Slightly low temperatures even as low as 94 degrees F. may be tolerated with no alarm. Hyperthermia, however, causes a deleterious effect and should be attended to promptly. With a rise of temperature rectally to 102.5 F. the following should be done. Strip the patient and sponge with a 50% alcohol solution in tepid water. Continuous evaporation by use of an electric fan

will help. In severe cases which are not altered by the above measures colonic instillation of cold tap water with siphonage in five minutes may be attempted. For stubborn situations ice packs and large doses of acetylsalycilic acid are used.

Bowel and Bladder. Catheterization with an indwelling tube attached to a tidal drainage system is used. The catheter should be changed every four or five days. Careful charting of intake and output is essential.

With severe incontinence of bowel enemata should be used to maintain a high degree of cleanliness.

Diet. The comatose patient should be maintained on intravenous fluids for 24-48 hours only. If not taking food orally by then, a Levine nasogastric tube should be passed. Feeding is instituted on an hourly basis. In successive hours give 120 c.c. of 5% glucose water, sweetened fruit juices and egg nog. Then repeat. Three grams of sodium chloride are added to the diet daily, The above schedule is continued throughout the 24 hour day.

Depending on the individual diagnosis other symptomatic and therapeutic measures will be added to the regimen.

The patient will continue on these measures with frequent re-examination and re-evaluation of his condition until such time as a cure is effected, surgery becomes necessary or death ensues.

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UPJOHN ABSTRACT: *The Drug Treatment of Hypertension;* Wolf, Robert L.; Mendlowitz, Milton; Weigl, Alfred; et al.; J. Mount Sinai Hosp. NY 28:191-195 (March-April) 1961.

An evaluation was made of all of the 167 patients in a hypertension outpatient clinic for a 3-year period ending June 1960. Primary hypertension was present in 152 patients, and 15 patients were treated for hypertension associated with chronic glomerulonephritis, chronic pyelonephritis, or renal artery obstruction. The results tend to show that drug treatment of primary hypertension should be started as early as possible.

The following antihypertensive drugs were used alone or in combination during this study: Rauwolfia derivatives, oral diuretics, ganglion-blocking agents, hydralazine, guanethidine, and bretylium tosylate. All drugs were given orally, and dosage was adjusted until the desired therapeutic effect was obtained or toxic symptoms appeared.

A good result was finally achieved in 45% of all cases of primary hypertension and a fair result in 27%. However, of the total of 458 antihypertensive regimens used in the 152 patients with primary hypertension, only 28% produced a good response and 27% a fair response. This shows that many different drugs and drug combinations must be tried to achieve a good to fair response in 72% of patients with primary hypertension. In the subgroup of 20 patients with mild primary hypertension, good results were attained in 75% and fair results in 20%.

In the 15 subjects with secondary hypertension, there were 3 good results, 5 fair results, and 7 poor results.

Rhythm, Emotion, and Periodic Psychiatric Illness

D. M. A. Freeman, 6T2

The concept of rhythmicity and periodicity as being important both in physiology and in disease is one to which perhaps little attention has been paid. It has exciting implications in psychiatry, both in understanding certain aspects of normal emotional function and in understanding certain uncommon but scientifically important psychiatric diseases. I would like to discuss the relation between rhythm and emotion, the effect of emotion on biological rhythms, some psychiatric correlates of biological rhythms, and finally focus the main part of my attention on the periodic psychoses. By approaching it in this order I will, I hope, be able to form a suitable background against which the periodic psychoses can be viewed.

Neurophysiology

Starting at the level of physiology, I would first like to mention the rhythmic nature of the central nervous system as a whole. The inherent rhythmicity of the individual neuron, and the rhythmic pulsating nature of overall central nervous system integration, as reflected in the EEG alpha pattern, are well known and will not be discussed in detail.

Rhythm and Emotion

Emotion may often manifest itself in a rhythmic way. This is not only true in the case of crippling fear, where trembling, shivering, and chattering of the teeth may occur, but also in several other emotions deeply felt. Beautiful music, or the "moment of truth" in a book or play may elicit shivering or "chills running up and down one's spine". Likewise, in a movement of deeply felt passion and intense love, shivering may become manifest. Experiences such as these may be familiar to you. Those described have been observed by myself and immediate friends.

A child may manifest insecurity by rocking, teeth-grinding, head banging, head nodding, or head rolling. An adult when he is tense may pace the floor.

Rhythm is important however, not only as an emotional manifestation in times of stress. A rocking chair for example, is an instrument which serves as a source of relaxation at times when we are at ease.

We respond to external rhythm from the very earliest stage. A mother, either simian or human, holds her baby with its head to her left breast. A group of investigators in Elmhurst, N.Y. wondered what connection this might have with the location of the mother's heart. The soothing effect of the sound of the relaxed mother's heart was found to be quite remarkable indeed. Crying was reduced by 50%, the infants actually gained weight in the first four days, and time required to fall asleep was cut to less than half. Other rhythmic activities which every mother knows are rocking, stroking, or walking, to calm an infant and put him to sleep. It might be added that an excited (i.e. fast) maternal heart sound was found to upset the infants and crying was immediately and noticeably increased. Lullabies seem to prolong rather than shorten the time required to fall asleep. The quality in addition to the frequency of the rhythmic sound is important. A metronome will not do, but a machine reproducing the sound of the uterine souffle works very well indeed.

As adults we respond to rhythm in a number of forms. Music is an example which is well known. Moods of tranquility or tension may be created with equal ease. One may take as an example the buildup of tension in the rhythm of a primitive rite. Somehow rhythm communicates to us and we respond. In music, one must of course separate out the effects of the melody and of habituation to certain forms. But it seems that rhythm itself has at least the *capacity* to communicate, for the pure rhythms of drums, of poetry, and of the singsong of religious recitation have their emotional effect. One might also mention the cross-cultural potency of this effect as evidence of the probable inborn nature of our response.

Adults create rhythmic activity for their own pleasure. This includes music, the rocking chair, dancing, and sex.

Psychosomatic Effects on Biological Rhythms

As the last part of our consideration of rhythm and emotion we might mention the impact of emotion on the biological rhythms (ie. hunger, sleep and menstruation). Psychosomatic effects such as in anorexia, insomnia, hypersomnia, amenorrhoea, pseudocyesis, and ovulation with the excitement of intercourse are well known.

In summary then, we find that the CNS has a rhythmic nature, that emotion has rhythmic manifestations and can influence biological rhythms, and that we create rhythm for our own pleasure and respond emotionally to external rhythm. One might wonder whether the latter phenomenon is due to a sympathetic resonance between the external rhythm and some internal rhythm. In any case, these phenomena form an important background against which the periodic psychiatric illnesses can be interpreted.

Periodic Psychiatric Manifestations

Periodic manifestations in psychiatry may be broken down into two groups: those which accompany the known biological rhythms (such as sleep, menstruation, and hibernation) and those which do not.

Related to the Biological rhythms

The first of the biological rhythms to be discussed is the *cycle of consciousness and sleep,* the cycle of night and day. A few facts have been known for some time. We all have our own patterns of consciousness and sleep, with the peaks of our efficiency curves at different times of day. To some extent these patterns are influenced by habit. It is found however that psychiatric disturbances are related to certain patterns. Those with depression tend to wake early and those with anxiety tend to have difficulty falling asleep. Depression tends characteristically to be deepest in the morning. Whether the sleep disturbance causes the psychiatric disturbance (which will be seen to be plausible in terms of work to be discussed below), whether the psychiatric disturbance causes the sleep disturbance, or whether both are merely symptomatic manifestations of underlying pathology is unknown.

Recent work by Kleitman and Dement in exploring dreams has cast exciting new perspectives on this whole field. Dreams are a cyclic biological phenomenon, present in humans after about the third extrauterine month, and probably in other animals too. The particular pattern of dreaming throughout the night varies from one individual to the next, but is fairly constant in the individual, and the total dreaming time is fairly constant from one individual to the next. They serve the psychological function of working out in symbolic and acceptable form the tensions, angers and hates that have accumulated during the day. The pertinacity of the inner drive of this rhythmic phenomenon is remarkable. It has long been known that sleep deprivation leads to hallucinations (which may be interpreted as dreams while awake) and even sometimes precipitates psychosis. Dream deprivation alone, without cutting short the duration of sleep as a whole, seems to lead to similar effects (though experiments in this have not been pushed as far). Subjects showed an increasing number of attempts to dream and a great burst of dreams when finally permitted to do so. Psychologically, in the daytime they manifested difficulty in concentration and memory lapses; tension, anxiety, irritability, and temper flurries. Several quit the experiment out of panic. Physically, most had a ravenous increase in appetite. Investigation in this field is only beginning. Alcoholic intoxication seems to have a similar effect of dream deprivation, by depression. Some go so far as to suggest this as a possible explanation of delerium tremens which they compare to the hallucinations of sleep deprivation. Schizophrenic dreams are strange: often they report nothing but an image of a single object such as a torn coat or an empty shelf, motionless in the air.

Another biological cycle with occasional psychiatric correlates is *the menstrual cycle.* The premenstrual tension syndrome, characterized by irritability, anxiety, depression, instability, and midly antisocial changes, is probably familiar. Its severity is directly related to the degree of premenstrual water and sodium retention and weight gain. One third of all women are affected to some degree. For instance the incidence of crime among Parisian women is found to be far greater during the premenstrual week than at any other time.

Another psychiatric correlate of the menstrual cycle is sometimes found in epilepsy. Hydration can sometimes trigger epilepsy, and epilepsy has psychiatric implications, particularly with temporal (limbic) lobe involvement. I have seen a case of limbic lobe epilepsy with monthly psychiatric exacerbations correlated with, and probably precipitated by, premenstrual hydration.

The final biological cycle about which obser-

vations along these lines have been made is *hibernation*. We probably retain some phylogenetic remnants of this cycle of seasonal variations in homeostatic adjustments. One study has reported a dominance of sympathetic tone in the summer, and parasympathetic tone in the winter. This alteration may be related to the reported seasonal fluctuations in manic-depressive, schizophrenic and periodic psychiatric illnesses. These include the illnesses about to be discussed. A seasonal incidence of suicide is also reported.

Independent of the Biological Rhythms

The Kleine-Levin syndrome consists of the triad of hypersomnia, bulima (increased hunger), and abnormal mental states, occurring in periodic episodes. The psychopathology in this syndrome consists of clouded sensorium, partial or total amnesia for certain periods of the attack, psychomotor retardation, and frequently a severe depressive affective disturbance. Sometimes included are autonomic, sensory, and motor symptoms. The pattern of the periodic episode *varies* from one case to the next, but *repeats* itself with each episode in the individual case. Thus this is a periodic syndrome with both psychic and somatic symptoms in which the cobmination and order of symptoms varies from case to case somewhat, but are repeated within the individual case. Many analogies will be noted between this and the periodic psychoses to be discussed below.

The cyclothymic personality has endogenous periodic swings in mood from depressive to "hypomanic", with or without intervals of normality between. In the hypomanic periods the patient feels well; in the depressive period he may have many minor somatic complaints, for which he will seek medical care. This condition may readily be confused with repeated reactive depressions. In the reactive type however, the depressions will follow stress of circumstances, whereas in the cyclothymic the depressions arise "out of the blue". The patient will be aware of their spontaneous nature himself. Cyclothymia often shows seasonal fluctuation, relating it to the hibernation question previously discussed.

There is a relation between cyclothymia and the *periodic psychoses*. Periodic psychoses are of two types; schizophrenic and affective, ie. periodic catatonia and periodic manic-depressive psychosis. Cyclothymics may never become psychotic or may become psychotics of either type. Sometimes cyclic psychoses may apparently arise without the person having been previously manifestly cyclothymic, but this is hard to prove. Mayer-Gross, et al, postulate the possibility that there is some endogenous cause of phasic variation in emotional life. When combined with an extroverted and cycloid temperament, this may give rise to cyclic manic depressive psychosis: when combined with a schizoid temperament, periodic catatonic schizophrenia may result. Crammer agrees with this approach and lumps all periodic psychotics together. In agreement with this approach is the observation by Gjessing that among the periodic catatonics he observed that the degree of regularity and suddenness of onset of the periodic manifestations is related to the degree of syntonic-pyknic ancestry, and that the degree of schizophrenic manifestation is related to the degree of schizoid ancestry. However Stokes points out that this may not be true, as some of the metabolic variations of periodic catatonia are absent in periodic manic-depressive psychosis.

The Periodic Psychoses

The periodic psychoses are very uncommon indeed. They are however of extreme interest to science, for in the fact that the same sequence of events occurs again and again in each period of the illness arises an incomparable opportunity for research. Each case can serve as its own control. Accompanying metabolic changes can be confirmed, as they occur repeatedly and predictably again and again. Furthermore, the influence of various precipitating, modifying, and therapeutic factors can be accurately assessed, by observing their effects to be the same each time they occur in separate cycles.

The periodic psychoses are characterized by periodically recurrent *psychic, somatic,* and *metabolic* events. The duration of the period varies from case to case, but is constant once established in the individual case. The periodic length is usually within the range of two to eight weeks (especially three to six). With a pattern of exacerbation and remission, the periods can be divided clinically into reactive and interval phases.

The interval phase is remarkably free of symptomatology, with only a lack of perspective, self-judgment, and understanding by the patient of his disease.

The reactive phase is composed of a mixture of psychic and somatic events. The patient passes from a cholinergic state (in the interval), through

a transitional labile phase, into an adrenergic state during the reactive phase. Accompanying this are the psychic manifestations which may be predominantly either manic (catatonic excitement), or depressive (catatonic stupor). Not infrequently however, elements of both types may be manifest. Gjessing found for example that many of his stupor cases passed through an excited or restless phase before, and a euphoric phase after the stuporous state; conversely, many of his excitement cases passed through a taciturn seclusive phase beforehand and an inhibited phase of low spirits afterwards. Crammer's observations were slightly different, as he thought that all cases passed through first an excited phase and then a depressed phase, with one or the other being most marked. His observations did, however, agree that frequently elements of both types of psychic reaction are present in the single patient.

What is most characteristic about this group of diseases is that these various elements are all present, though their order of appearance and relative preponderance varies, like the length of the period, from case to case, and tend to remain fixed as a constant pattern in the individual case once the pattern has become established.

It has been pointed out that regardless of the clinical symptomatology the individual passes into an *adrenergic* state. About the only marked difference between stuporous and excited patients in this regard is the presence of oily skin secretion and thick stringy mucus in former (stuporous) case. Likewise the *symptoms* experienced by the individual are essentially the same whether in a stupor or excitement state.

Something should be said about the delimitation and definition of the group we are discussing. The onset of the reactive phase may be more or less sudden, and the regularity more or less marked. It is the more *regular* type with the more *abrupt* onset that we are considering here, to which Gjessing gave the name "synchronous—syntonic". (As mentioned above, he found the degree of this cyclic regularity related to the degree of syntonic-pyknic ancestry).

We have then a group of components, ordered in a variable arrangement, with the pattern being however a "fingerprint" characteristic of the individual case. These components include not only psychic events, but also physiologic and metabolic events. The group of diseases vary in length of period, content of psychopathology (ie., whether predominantly affective or schizoid), and the particular orchestration and sequence in which their metabolic, physiologic, and psychic disturbances are manifest. The onset may be with a periodic pattern right from the start, or the periodic pattern may develop afer an endogenous depression or schizophrenic disorder has been present for some time. In younger individuals, the disease may occasionally spontaneously and permanently remit.

Metabolically, phasic variations have been observed in cellular nitrogen retention, in salt and water retention and weight gain (cf. premenstrual tension), in acid-base balance, and in some cases in steroid metabolism. As has been pointed out, none of these metabolic cycles, though they have the same period length, is necessarily *in phase* with either the reactive-vegetative clinical cycle or with each other. Of these metabolic changes, the weight changes which accompany water retention are very simply available to clinical observation and therefore serve as an important diagnostic sign.

Some of the best work in this field has been done at the Toronto Psychiatric Hospital, where an intensive study of this group of diseases has been going on for years (Dr. Stokes, Dr. Lovett-Doust, Dr. Bonkilo). The approach is to study single cases in tremendous detail over a long period of time. Some of the metabolic observations mentioned above were made here, and one or two physiologic ones might be mentioned. Capillary blood anoxemia is present in either type of reactive phase (excited or stuporous). In the EEG, alpha wave incidence and amplitude both decrease sharply with the onset of the disturbed phase. Alpha frequency however seems to vary in an interesting way according to a few cases. It increases in either an anxious irritable stupor or in excitement, but decreases in a docile, placcid, fantasy type of stupor which is filled with wish-fulfilling dreams.

Irregularities and Intercurrent Factors

It should be recalled that no biological rhythm takes a strictly predictable mathematical form. Menstruation for instance is never exactly predictable as to time of onset and duration. Intercurrent factors have an effect. The effect of emotions causing irregularities such as amenorrhoea, premature ovulation, and pseudocyesis has been discussed, as have effects on the diurnal sleep cycle. Despite some irregularities we are able to discern an underlying *regularity,* and therefore

we interpret these phenomena as basically rhythmic, and the fluctuations as ascribable to endegenous and exogenous intercurrent factors. The same is true of the periodic psychoses.

Furthermore, in addition to the fact that a basic regularity can be observed in the periodic psychoses, supporting evidence is to be gained from a study of the cases in depth. For it is found that whereas there may be fluctuations in the clinical picture to the extent of complete absence of symptoms at a time when they are due, or prolongation of a single reactive phase without remission for several period lengths; nevertheless, metabolic and physiologic observations show that the cyclic pattern is still *continuing*. It may however, not break through every time into clinical symptomatology, or the symptomatology may not always remit sufficiently to show a clinical interval phase.

Seasonal fluctuations represent interference from a known biological rhythm. Some cases have attacks which increase in strength from autumn on, reaching a peak in January before declining. In others, the incidence of skipped periods (which amounts essentially to the same thing) shows a seasonal pattern. In cyclothymia and in nonperiodic psychoses in general, such seasonal fluctuations may also be observed. It seems likely that the fluctuations are in the extent of psychopathological manifestations rather than in the underlying cyclic pattern. Perhaps closely allied is the fact that marked weather fluctuations seem to have an effect. I group these together with seasonal fluctuations as both may conceivably be manifestations of the hibernation mechanism whereby homeostasis is adjusted to climate. In some cases the onset of the reactive phase occurs more frequently than by chance concurrent with sudden changes in temperature, moisture and pressure.

Other intercurrent factors are infections which sometimes coincide with the original onset of the disease, diet (which was standardized by Gjessing as part of his therapeutic programme), and certain therapeutic procedures.

Therapeutically, Gjessing found that by starting thyroid therapy at a certain phase of the nitrogen cycle, by building up rapidly to toxic doses, and then dropping to a maintenance level along with standard diet and stable environment, he was able to suppress both the nitrogen cycle and the *psychic clinical* aspects of the disease. It did *not* suppress the underlying cyclic changes however, which were still observable by some of the physiologic and metabolic tests, and unless the disease entered a spontaneous remission, the psychic phenomena would start again at an exactly predictable phase once the treatment was stopped. ECT and chlorpromazine are other exogenous intercurrent factors which may be used therapeutically. Crammer believes that the latter may interrupt the cycle as a whole.

Discussion

We have then a complex orchestration of metabolic, physiologic, and psychic events recurring periodically with some variation in the relative proportions and sequence of the components. One might try to explain it in several possible ways. It could conceivably all be *psychogenic;* it might simply be a *vicious circle,* which once initiated kept going on because of one event precipitating the next, as an attempt at homeostatic adjustment; or it could be that there is some *endogenous pacemaker* which rhythmically causes disturbances in various systems. The first of these alternatives is unacceptable as it has been shown that it is possible to interrupt the psychic phenomena with thyroid suppression of the N-cycle without interrupting the rhythmicity. Likewise skipped periods may spontaneously occur when there are no clinical psychic manifestations, but the periodic metabolic changes continue. The second type of interpretation, on the theory of a vicious circle, does not seem correct for the same reasons, as it seems possible by therapy to interrupt certain parts of the cycle without changing the cycle as a whole. Some periodic changes will continue even in the absence of others, and it has been shown that after long periods of suppressive thyroid therapy the cyclic psychic pheneomena recur in an exactly predictable phase, when therapy is stopped.

It seems then most likely that there is an *endogenous pacemaker* of a given periodicity which causes changes, though not necessarily concurrent ones, in several systems. Zondek argues that this pacemaker is most likely located in the *hypothalamus* and that the various mental and physical phenomena are coordinated by this pacemaker rather than causally connected to one another. He points out that hypothalamic regulation is rhythmic in character as evidenced by the rhythmicity of various functions under its control such as sleep, respiration and menstruation. Furthermore the hypothalamus is connected with emotion through the limbic lobe. Gjessing also theorizes that the hypothalamus is the location of the pacemaker, and suggests that it might be of the nature of an intoxication by the accumula-

tion of some *substance*. This would explain the variation between individuals in period length, as such a toxic metabolite might be formed more rapidly in one individual than another and individual susceptibilty to its effects might vary. Also, the susceptibility of various parts of the hypothalamus might vary, explaining the variation in the orchestration of the components of the attack from one individual to the next. This then seems to be a comprehensive theory, plausible in terms of the knowledge we have, but by no means demonstrated yet.

It has been pointed out that these conditions offer an excellent opportunity for research, providing their own controls. Useful investigations can be done here and hypotheses found for the broader field of psychosis in general. No quick generalizations can be drawn without experimental demonstration in each case however, as it is difficult to know whether a metabolic concomitant, or response to stress or therapy observed here is due to the peculiar cyclic nature of *these* diseases or to something broader which they share *in common* with all schizophrenias or manic depressive psychoses. Thus, the fact that these diseases are almost certainly endogenous does not necessarily shed light on the argument of whether all schizophrenias or manic depressive psychoses are endogenous as opposed to psychogenic.

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Book Review

Postpartum Psychiatric Problems. by James A. Hamilton, Ph.D., M.D., C.V. Mosby Co., St. Louis. 1962. 156 pp. $6.85.

Postpartum psychiatric illness is a distressing problem which effects a woman at one of the most rewarding times in her life. She is praised by society for having successfully brought a human being into the world, and at the same time she is accutely needed by this tiny being. Psychiatric illness cancels all ideas of praise and sometimes threatens the life of the infant.

This type of illness is not associated exclusively with any one specialty, but cuts across the fields of both obstetrics and psychiatry. Because of this, the disease entity is not fully understood, and there is often confusion between both branches of medicine. Dr. Hamilton in his book has gathered and organized material from various sources which is related to postpartum psychiatric illness, to clarify the problems involved.

In a typical case, the new mother is perfectly well for two days. On the third day, either sudden or insidious changes are seen in her personality. She becomes anxious, confused, energy and sex desire are decreased, and sometimes delerium results. The attending physician or obstetrician must be alert to the possibilities of psychiatric disturbances, because one in a thousand postpartum females have a very severe illness. Usually a psychiatrist is notified after a valuable length of time. His diagnosis however, is made from symptoms alone, and usually falls into one of three categories: delerium, affective disorders, or schizophrenia.

Dr. Hamilton suggests that postpartum psychiatric illness is diagnosed and treated too much like psychiatric disorders not associated with pregnancy. He feels that the physiological aspects of the postpartum disorders play as large a role as psychological factors which are though to 'trigger' the psychiatric illness The 'third day blues', common after all childbirths, is seen by some as a mild form of postpartum psychiatric disorder, pointing to a common factor of some kind (organic or psychological).

The confusion and delerium of these disorders are indicative of organic disease, and some studies done on factors operating before childbirth tend to indicate a non-psychological etiology. Deficits of thyroid and pituitary hormones and excesses of adrenal cortical hormone are discussed as possible etiological factors. Thyroid treatment empirically has helped a significant percentage of patients when it was tried. An abnormal uterine mucosa was seen in some patients with postpartum psychiatric disturbances.

Dr. Hamilton's book, although small, is a complete summary of the work done in postpartum psychiatric problems. He makes no bones about the fact that many of the observations and inferences about these conditions were made many years ago, and that further research is badly needed. Full bibliographies are included after each chapter for interested persons. This book, in addition to being interesting and stimulating to any student or medical practitioner, is a *must* for budding obstetricians and psychiatrists.

Problems in Surgery. by Frank Glenn M.D. and George Wantz M.D., C.V. Mosby Co., St. Louis. 1961. 512 pp., illustrated. $16.50.

Problems in Surgery is a different type of surgery book which was compiled from Saturday morning grand rounds of the Department of Surgery of the New York Hospital — Cornell Medical Centre. A series of 152 cases were selected from tape recordings of these sessions. They are organized according to the branch of surgery involved, from pulmonary to orthopedic, but no attempt is made to attain any degree of completeness. The cases vary from the common (case 67 — Intrahepatic jaundice versus extraphepatic jaundice), through the unlikely, to the 'birdy' (case 92 — Arteriovenous fistula between the internal carotid artery and the cavernous sinus folling skull fracture). All cases are interesting and were selected because they represented some special or recurrent problem in surgery.

Each case is presented as it would be at rounds. The initial history and physical findings are written as a resident would present them. Radiological findings, where relevant, are then reviewed and shown as a photograph in most cases. Discussion follows. The participants in the discussion are senior members of the surgery staff, members of other specialties, visiting dignitaries, residents and students. The voice of the student is very small. I could find only two quotes by students, but both are learned questions. Each case was edited. adding material for completeness and subtracting irrelevant comments. It is assumed that any fights or jokes were omitted to aid unity of thought.

If fights were omitted, differences of opinion were not. Specialists in the various fields give their opinions freely, and many trained minds operate to bring relevant facts to a particular problem. Dr. Glenn, Cornell's professor of surgery, acts as moderator in most cases, and asks many searching questions to help preserve the spirit of enquiry.

This book makes interesting reading but is not recommended for the 'crammer' who probably prefers to have *all* the salient facts presented to him in point form. J.D.G.

DIAGNOSTIC RADIOLOGY

Figure 1. What is your diagnosis and the complications of this lesion? What other views should you have when searching for it?

Figure 3. This 61 year old lady had a two month history of frequency, haematuria, and clots. What do you see in this film?

Figure 2. This fracture was sustained by a 71 year old female by slipping on the bathroom floor. What is your diagnosis and treatment?

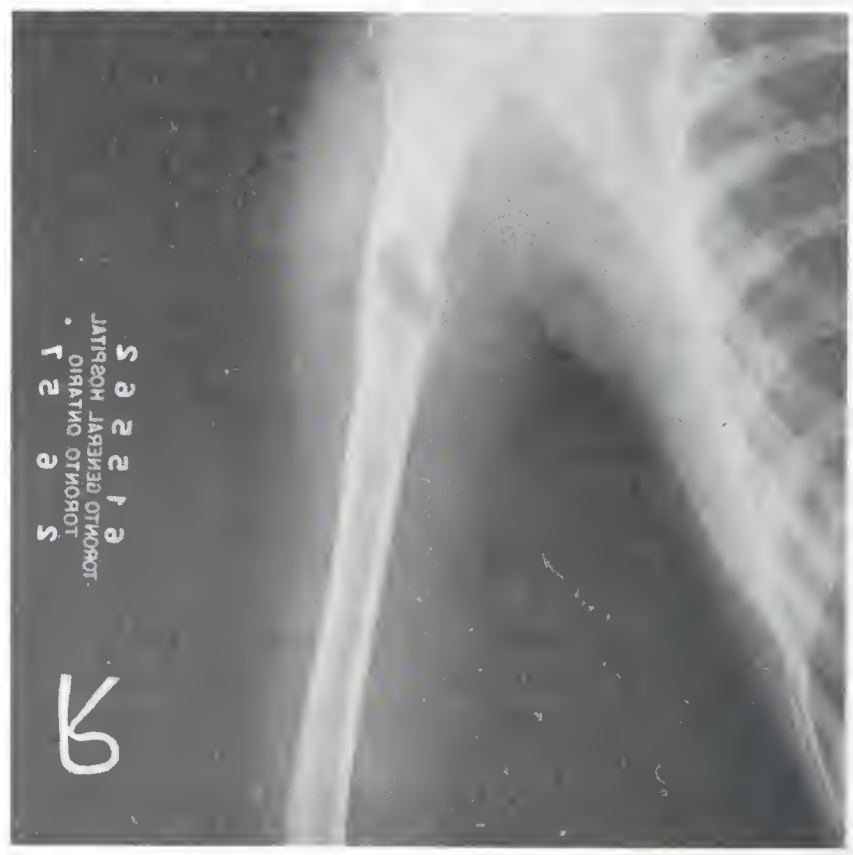


Figure 4. This 12 year old girl complained of gradually increasing local pain and swelling in the right arm. The AP view showed a moth-eaten appearance at the site of the lesion. What is your diagnosis?

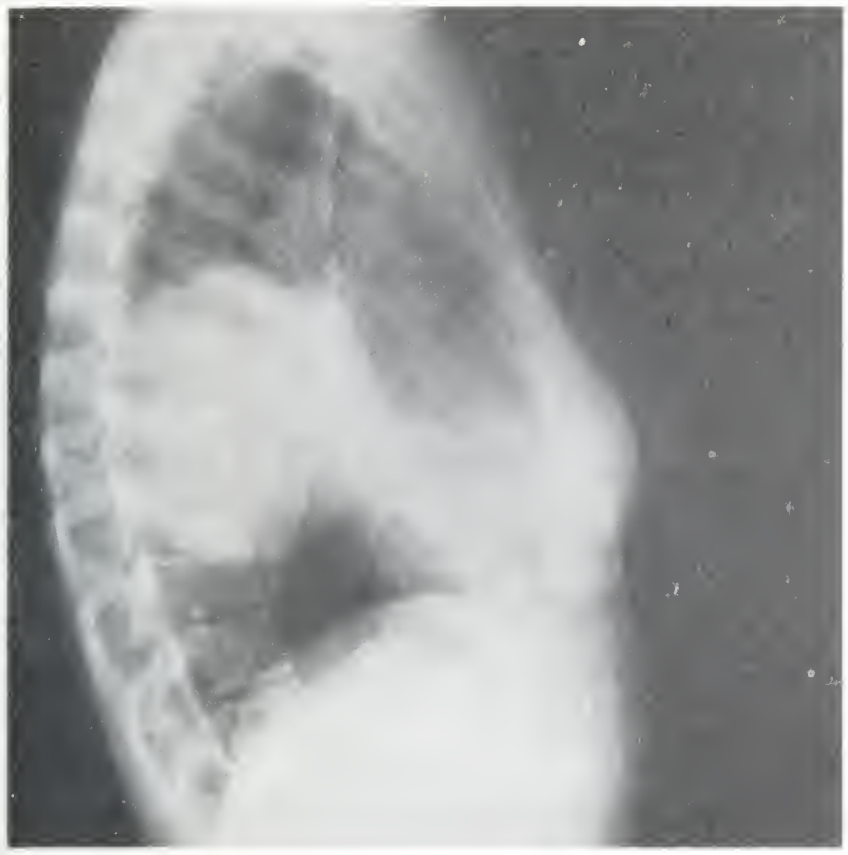


Figure 5. The opacity in the left chest was found on follow-up examinations of a 14 year old girl who had had an amputation of an arm. What is it?

Figure 7. What do you observe in the pelvis of this 51 year old male?

Figure 6. Treated twice previously with urethral dilatation, this 60 year old male complained of poor stream and dysuria for one week. What would your report on this film be?

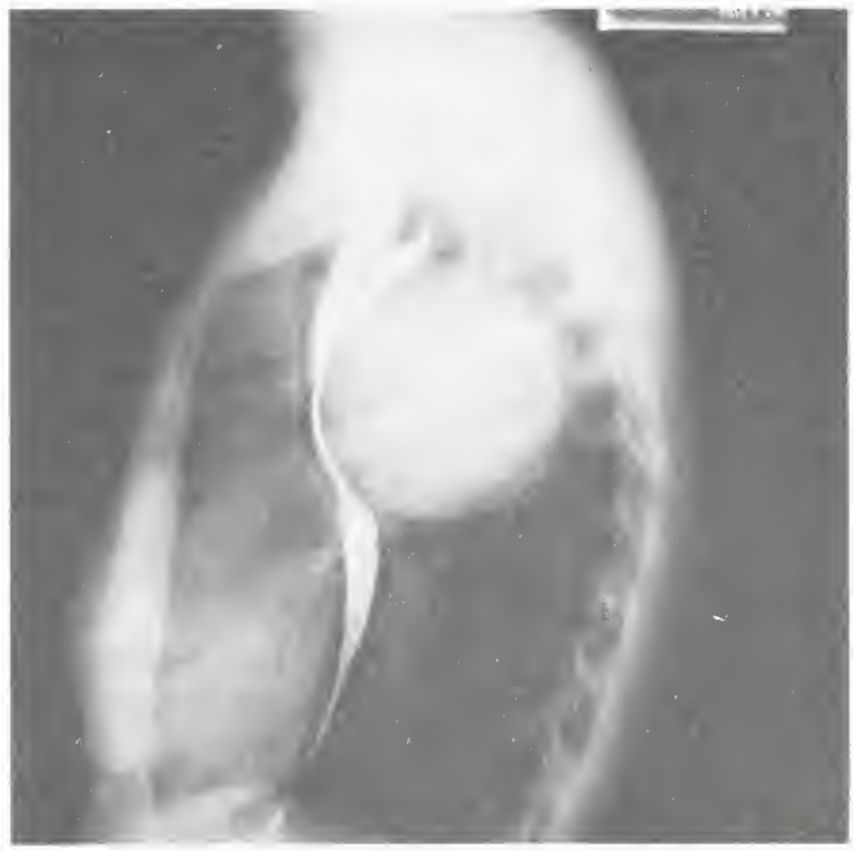
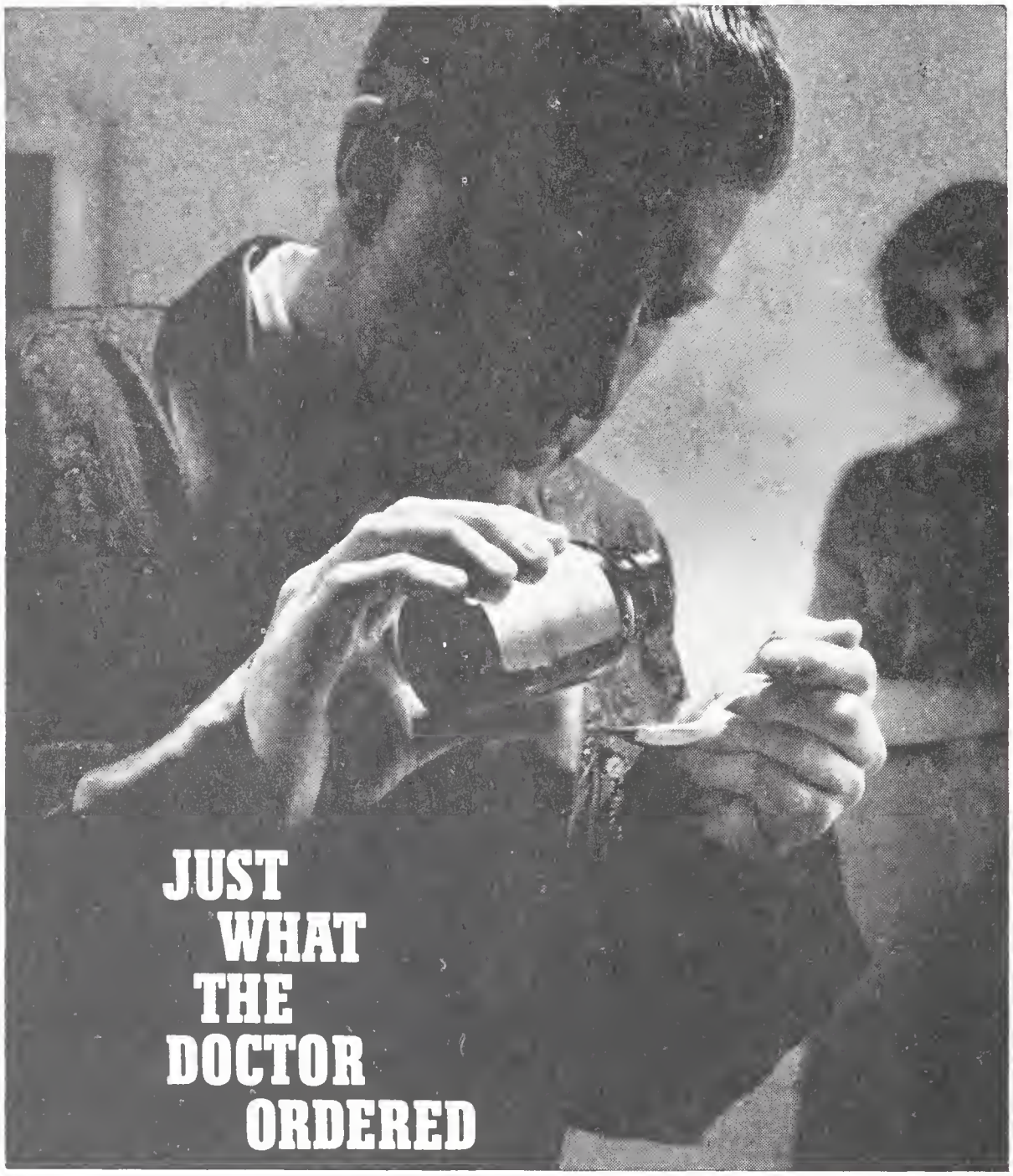


Figure 8. What do you see in this film of a 45 year old female and what is your diagnosis?

For Answers to Diagnostic Radiology turn to page 233.



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Chronic Irreversible Allergic Tissue Injury

by R. Baumal, 6T3

It is generally believed that human diseases such as glomerulonephritis, rheumatic fever, and perhaps polyarteritis nodosa and other collagen diseases, have an allergic etiology (i.e. that they are somehow caused by interaction of antigen and antibody). Support for this contention is found when experimental animals are injected with foreign protein (antigen) [13-17]. Renal, cardiac and arterial lesions morphologically identical to their human counterparts are produced. Antibodies are demonstrable in the serum. However, the actual mechanisms of tissue destruction are obscure.

The above human diseases may produce a transient (reversible) tissue injury and later become completely resolved, leaving no evidence of prior damage. More important is their tendency to become chronic (irreversible) in some individuals and produce perpetuating tissue damage terminating in death.

In recent years a workable theory has been proposed by Dixon to explain the mechanism of transient or reversible tissue injury[5,6]. No one has yet been able to explain why in some cases tissue lesions become completely resolved, and why in others they go on to chronicity, scarring and permanency.

The Dynamics of Reversible Tissue Injury

(according to Dixon) [5,6]

Dixon made use of the following facts to explain the pathogenesis of reversible tissue injury: (1) the intravenous injection of a *moderate amount* of a foreign protein initiates the cycle of active and specific antibody synthesis; (2) the foreign protein (antigen) is dealt with in three distinct phases: (a) a phase of *equilibration* in which the antigen becomes evenly distributed in the intra- and extravascular compartments; (b) a phase of *normal catabolism* in which the foreign protein is handled by the organism in the same manner as a corresponding endogenous protein, and (c) a phase of accelerated *immune catabolism,* commencing at the time of appearance of antibody in the circulation, and lasting until total antigen elimination from the circulation has been achieved, and free, circulating antibody makes its appearance. Since antibody production rises gradually, *antigen-antibody complexes form in the circulation in relative antigen excess.* This phase is all-important, since it is during this time interval that the inflammatory allergic tissue lesions make their appearance. (3) localization of antigen and probably of antibody at the sites of the lesions (glomeruli, endocardium and arteries) occurs immediately after their interaction in the circulation. No antigen becomes fixed to tissues prior to the development of antibody.

Based upon these facts the following theory was formulated. Following the intravenous injection of an antigen, antibody makes its appearance, and combines with the antigen in the circulation in an excess antigen environment. The resulting antigen-antibody complexes increase in amount in parallel with increasing antibody synthesis and are subsequently eliminated when all free antigen in the circulation has been used up in the formation of such aggregates. The immune elimination of antigen depends upon: (1) the rapidity of antibody formation, (2) the quantity of available antigen, and (3) the quality of the antibody produced. These complexes formed in antigen excess are presumably capable of initiating inflammatory responses in the endocardium, glomeruli and certain arteries. This they do by their inherent phlogistic potential; they penetrate the endothelial and intimal vascular barrier and evoke a non-specific proliferative inflammatory response. The reasons for the localization of the allergic inflammatory lesions at these specific sites remain obscure. The inflammatory reaction progresses simultaneously with the concentration of complexes in these sites, and the lesions promptly regress following total antigen elimination from the circulation. The antigen and antibody in the lesions then become catabolized, and the injury repaired (i.e., the effect is entirely reversible).

It should be added that this theory, dealing as it does with an animal which has had no prior contact with the antigen, adopts the view that immune complexes formed in antigen excess are only damaging upon *entry into the tissues* of the

specific site of injury. Failure to localize here results in a total absence of lesions.

In Vitro Preparation of Antigen-Antibody Complexes[12]

The affinity of antigen and precipitating antibody for each other can be examined in vitro. The formation of a visible reaction (i.e., the formation of a precipitate) is taken as evidence of their combining power. However, immune complexes form in various reciprocal proportions of antigen and antibody, and they may form molecular aggregates insufficient in size to be seen with the naked eye. These latter types of aggregates are referred to as *soluble immune complexes,* and they form when antigen and antibody combine in marked excess of either component of the complex. Those forming when optimal proportions of antigen and antibody are present leading to visible precipitation (in the zone of equivalence) are referred to as *precipitated immune complexes*. In actual fact, however, the zone of equivalence is located in slight antibody excess. Tests of the pathogenicity of these immune aggregates have been carried out using all three types of complexes, i.e., those formed in various amounts of antigen excess, those in various amounts of antibody excess, and those formed at equivalence.

Toxicity of Preformed Soluble Antigen-Antibody Complexes in Antigen Excess

Dixon's theory presupposes that soluble antigen-antibody complexes in antigen excess possess an inherent toxic potential in tissues. This is now known to be true. Such complexes produce systemic anaphylaxis upon intravenous injection into guinea pigs[9], mice[20] and rabbits[22] and cause contraction of isolated smooth muscle in the Schultz-Dale reaction[21]. They cause an increase in vascular permeability when injected into the skin of guinea pigs[11] and lead to liver cell necrosis when injected in to the portal vein[18]. Benacerraf et al.[1-3] injected soluble antigen-antibody complexes in antigen excess into mice, and produced severe acute glomerulonephritis, necrotizing arteritis, and acute endocarditis. All lesions developed within 36 hours after the first of three injections of complex and disappeared completely within two weeks. This was proof-positive that Dixon's assumptions were correct.

The Role of Precipitated Antigen-Antibody Complexes at Equivalence[19]

Our work has been concerned with precipitated antigen-antibody complexes formed in the zone of equivalence. The injection of such complexes into the skin of rabbits has shown that an immediate acute inflammatory reaction around the precipitated acidophilic protein complex is followed by necrosis and by a gradual replacement of the initial polymorphonuclear reaction by a mononuclear one. When fluorescent-labelled antigen is used in the preparation of the complex, it was not found beyond the confines of the initial area of aggregation in tissues. Thus the occasional vascular lesions (e.g., mild vasculitis and thrombosis) were considered to be secondary to the necrotizing injury in connective tissue and muscle. At the conclusion of 8 days, mature plasma cells made their appearance particularly in the adventitia of small venules and around peripheral nerve fibres. From about the 8th day onward there was, in the majority of animals, a massive proliferation of granulation tissue, ultimately replacing almost entirely the site of the lesion (organization). This is in marked contrast to the ultimate fate of lesions produced by soluble immune complexes in antigen excess where little evidence of injury remains at the conclusion of 9 days (i.e., complete resolution)[4].

The importance of these experiments is underlined by an insignificant reaction (slight edema and occasional polymorphonuclear leucocytes in dermis) produced by the various antigens alone, and the various homologous antisera alone respectively. *One may therefore conclude that precipitation of a foreign antigen by means of an inert homologous antibody brought in contact with tissues in large concentration and for a prolonged period of time produces tissue destruction followed by fibrosis.*

A Concept of the Mechanism of Irreversible Tissue Injury

Upon intravenous injection of a *moderate to large amount* of an antigen, systemic antibody production is induced. When the circulating level of antibody allows the formation of soluble antigen-antibody complexes in an antigen excess medium, such immune aggregates penetrate the endothelial and intimal barriers of arteries, endocardium and glomeruli and initiate an acute inflammatory reaction. This response, due to the greater amount of antigen available than that present in reversible tissue injury, is characterized also by the simultaneous initiation of the local maturation of plasma cells deeper within the connective tissue. These cells and some of their pre-

cursors commence to produce antibody locally *except in the glomerulus* where there are no plasma cell precursors.

If a second dose of antigen is administered at the time, locally maturing plasma cells are available at the site of lesions, or if a single large dose of antigen was used initially, new toxic complexes begin to be formed in the circulation at an accelerated rate. They again enter the designated tissues. These have now reached the stage of hypersensitivity (altered immunologic reactivity), i.e., appropriately attuned immunologically competent cells are available to produce antibody locally within probably 24 hours or earlier, following contact with the newly arrived immune complexes. This is known as a secondary immune response. (If a large dose of antigen had been used, no lag would occur). Localization of the complexes formed in antigen excess may begin to be appreciably influenced by locally produced antibody which, upon interacting with the complex, would tend to create antigen-antibody proportions closer to or at equivalence.

In an appropriately responsive animal all subsequent entry of soluble complexes into tissues would be met by increasing amounts of locally produced antibody. Precipitation of antigen would be favoured and retention of antigen in tissues ensured. Evidence has been produced that antigen retained in tissues for a sufficiently prolonged period of time in a sufficiently high concentration is phlogistic in itself and produces an injury terminating in fibrosis.

Additional Considerations.

A further factor enters into the determination of the persistence of lesions. If the above reasoning was correct, then we should expect fewer and less severe arterial or endocardial lesions with an easily catabolizable antigen than with one whose half-life is longer. Germuth et al.[8,10] have shown that bovine gamma globulin, a more rapidly catabolized protein (half-life 2 days) than bovine albumin (half-life 4-5 days) produces fewer arterial lesions than the latter antigen. Thus, bovine albumin would stay in contact with tissues longer and in higher concentration than bovine gamma globulin. Germuth et al. showed later that the handicap of a shorter half-life of bovine gamma globulin could be overcome by repeated injections, ensuring a more constant concentration of antigen in contact with tissues. In these circumstances arterial lesions become as common as with bovine albumin.

The systemic antibody-producing capacity of the animal has a major bearing upon the development of chronic lesions[7]. Using rabbits as experimental animals, it was found that upon repeated daily antigenic challenge, these fit into three immunologic groupings: (1) those with no detectable circulating antibody; (2) those which produce great amounts of antibody; (3) those whose antibody production is barely sufficient to combine with the available foreign protein. Animals of Group 1 produce no lesions; those of Group 2 produce acute transient arteritis and glomerulonephritis. Such animals upon first injection would produce large quantities of soluble complexes in antigen excess for a brief period of time only, as immune catabolism is greatly accelerated. Hence, the time of contract between tissues and antigen would be reduced. However, although upon subsequent challenge these animals would produce complexes near equivalence in the circulation, these would be unable to perpetuate tissue injury because little, if any, prior tissue damage to the endothelial and intimal vascular barrier would have been inflicted. Owing to their size, the precipitated complexes would tend to be phagocytosed by the reticulo-endothelial system, and thereby inactivated. Animals of Group 3 produce severe subacute or chronic arteritis and glomerulonephritis. In these animals receiving a daily small injection of antigen, conditions would favour a daily recurring soluble complex injury to the endothelial an intimal vascular barrier. Hence soluble complexes are able to continually penetrate tissues and be modified by locally produced antibody, thereby forming *within tissues,* complexes close to or at equivalence. By this method, antigen is maintained in contact with tissues for a longer time.

We have stated that the glomerulus cannot be included in the above concept of irreversible allergic tissue injury because there are no plasma cells or plasma cell precursors at this site. The modifying influence of locally produced antibody is not available here as in arteries and in the heart, and consequently, has no bearing upon the injury. How then can we account for the retention of antigen in glomeruli? (What are the factors determining chronicity of such lesions in the glomerulus?). Two explanations are available.

Benacerraf et al. suggested that, if during dissociation and re-association of soluble complexes at the basement membrane barrier, free antigen was to pass the filter at a rate faster than the complex bound-antibody, conditions favouring pre-

cipitation would develop since equivalence proportions may be created. At the glomerular filtration barrier, precipitation would be the result of a decrease in antigen.

With increasing antibody production in the secondary immune response, sufficient antibody may be produced to lead to near equivalence conditions in the circulation. Although most of such large immune lattices would be treated as colloidal particles and phagocytosed by the littoral cells of the reticulo-endothelial system, some may become localized in glomeruli, particularly if prior injury by soluble complexes had prepared the ground. Whatever the mechanism which leads to antigen precipitation in glomeruli, the end result is similar to that in other sites. Persistence of antigen leads to reparative processes which culminate in glomerular obsolescence.

In summary, we suggest that with large amounts of antigen, "toxic" soluble immune aggregates enter hypersensitive tissues and are there modified by locally produced antibody. The *phlogistic effect may no longer be dependent from then onward upon the toxocity of immune complexes, but upon the persistence (retention) of their antigenic component in contact with tissues.* This may well be "the yet unidentified non-immunologic factor" of chronic allergic inflammation postulated by Dixon et al. to account for the permanency or irreversibility of tissue injury[7].

Factors determining the Character of Allergic Tissue Lesions

In accordance with the above concepts, the following factors may play a role in determining the character of allergic tissue lesions.

Factors favouring an Evanescent Outcome (Reversible Tissue Injury).

(1) The presence of a limited quantity of circulating antigen;

(2) an antigen with a short catabolic half-life;

(3) the ability of the recipient animal to produce a large quantity of circulating antibody;

(4) the formation of soluble circulating antigen-antibody complexes in antigen excess;

(5) the entry of such complexes into the specific sites of injury;

(6) the absence of locally produced antibody;

(7) the rapid removal of antigen from the tissues.

Factors favouring a Persistent Outcome (Irreversible Tissue Injury).

(1) The presence of a depot of antigen in the circulation, sufficient to induce a local as well as a systemic antibody response;

(2) an antigen with a long catabolic half-life;

(3) the ability of the recipient animal to produce circulating antibody in amounts barely sufficient to neutralize the antigen;

(4) the formation of soluble circulating antigen-antibody complexes in antigen excess, or near equivalence;

(5) the entry of such complexes into the specific sites of injury;

(6) the presence of locally produced antibody;

(7) the aggregation of antigen in tissues.

Since all the above factors constitute variables, it is understandable that the outcome of the injury in morphologic terms should be extremely difficult to relate in detail to each one of the factors individually.

Summary

Dixon's explanation of reversible tissue injury and supporting evidence for his theory have been reviewed. Since this theory did not explain the factors which determine progression of the evanescent lesions to chronicity and fibrosis, we have presented a concept of the probable mechanism of this latter type of injury. We have established that many factors are operative in this respect, and we have suggested that the most important of these may be an *inherent toxicity of aggregated foreign protein.* We have arrived at this conclusion by assigning to antibody not only an *active role* in producing injury by the formation of phlogistic antigen antibody complexes, but also an incidental, *passive one* in that it tends to retain antigen in contact with tissue in sufficient concentration, and for an adequate period of time to allow the inherent phlogistic potential of the antigen to become apparent.

ACKNOWLEDGMENT:—I wish to thank sincerely Dr. J. W. Steiner, Assistant Professor of Pathology, University of Toronto, for his co-operation.

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UPJOHN ABSTRACT. Subject: *Steroids in Cirrhosis.* Long-Term Treatment of Cirrhosis of the Liver with Prednisone. Harvald, Bent; Madsen, Sten (Medical Dept. C, Bispebjerg Hosp. and Dept. III, Kommunehospitalet, Copenhagen, Denmark). Acta Med. Scand. 169:381-387 (April) 1961

Continuous long-term treatment with prednisone in 66 patients with different forms of cirrhosis of the liver was very effective in those with postnecrotic cirrhosis, less effective in those with biliary cirrhosis, and ineffective in most of those with portal cirrhosis.

Of the 66 patients, 48 had postnecrotic, 10 had portal, 7 had biliary, and 1 had teleangiectatic cirrhosis. The authors note that serum transaminase activity appears to be a sensitive indicator of liver cell damage; repeated determinations of this activity during treatment can probably provide a valuable indication of the optimal steroid dosage required to control symptoms.

The group of patients with postnecrotic disease improved symptomatically and also survived much longer than had a group of 89 comparable patients who, during an earlier period at this same hospital were not treated with steroids, Among treated patients the survival rate after 3 years was 62.7% among untreated patients it had been 21.5%. In 11 of the present 48 cases, it was possible to discontinue prednisone therapy without a recurrence of symptoms; however, it still is not certain whether the results will be lasting.

The comparatively few side effects caused by treatment included perforation of an undiagnosed gastric ulcer in a 60-year-old woman; slight, generally temporary glycosuria in a few patients; moon face in a number of cases; and some slight hypertension in a few cases. A 78-year-old woman with biliary cirrhosis of several years' duration suffered a spontaneous fracture of the spine after 2 months of prednisone therapy, but the occurence could not be attributed unequivocally to medication.

UPJOHN ABSTRACT: *Recent Trends in Therapy of Cerebral Vascular Disease;* Groch, Sigmund N.; Wright, Irving S. Circulation 23:458-465 (March) 1961.

This discussion of the various measures available for treating a patient with a stroke is quite largely concerned with anticoagulant therapy. It seems most efficacious in treating recurrent transient ischemic attacks and the slowly progressive stroke. Its value in the acute phase of cerebral thrombosis and in long-term postinfarction therapy is not yet clear. Its role in cerebral embolism seems to be well established; the authors usually withhold anticoagulants for 24 to 36 hours after an acute cerebral embolus and do not administer anticoagulants in the presence of a xanthochromic cerebral spinal fluid. They also believe that it is dangerous to use anticoagulants in the presence of severe hypertension. There are certain well-defined syndromes in which surgical procedures are promising. The prognosis is poor for massive intracerebral hemorrhage, except for those few patients in whom spectacular improvement follows neurosurgical evacuation of an intracerebral hematoma. Subarachnoid hemorrhage has a better prognosis when treated suitably with surgery.

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Malignant Melanoma

by R. P. Humphreys, 6T2

Man's efforts to obtain the bronzing rays of the sun each summer in order to enhance his personal appearance, are in curious paradox to those of lower animals where the same physiological process is probably involved in protecting that animal from his predators. For it is believed that the mechanism which produces the spotting of animals and camouflaging coat is related to the complex pigmentary schema which man possesses in his own body. The purpose of this presentation then, will be to outline the normal physiological processes involved in that schema, and then to illustrate what happens when that process somehow goes awry to produce one of the most insidious malignancies known to medicine. Some attempts will also be made to outline current methods of treatment.

Physiology

The colour of one's skin depends not only on the degree of pigment contained therein, but also on the vascularity and depth of subcutaneous tissue; however, it is with the pigment that we are primarily concerned. This pigment, known as *melanin,* is elaborated by a complex sequence of events whose full ramifications are still not entirely understood. Melanin can be found both in the epidermis and the dermis. In the former, it lies as brown to black granules in the cytoplasm of the cells (*melanoblasts*) in the deep layer of the epidermis (stratum germinativum), usually situated between the outside world and the nucleus of that cell (Fig. I). The pigment is also found in the dermis, but to a lesser degree, and there it is thought to exist almost exclusively as a substance phagocytized by chromatophores, which take up residence in the dermis. One exception is seen to this, and will be mentioned later.

Melanin is thought to originate from the clear

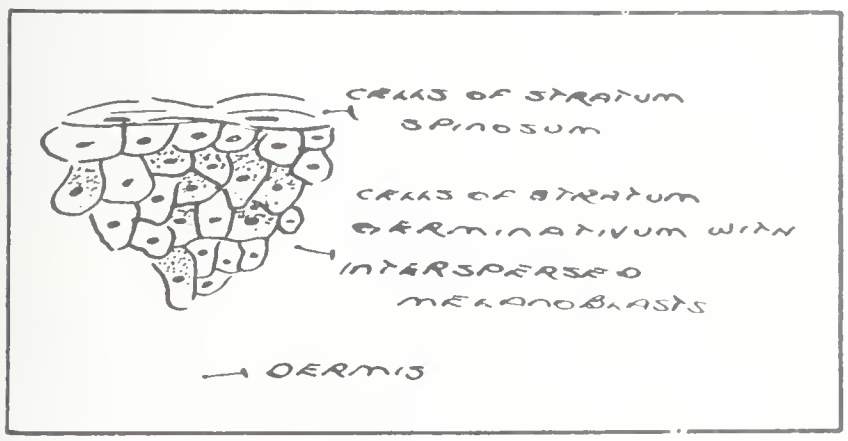

Fig. I

cells which lie either between the cells of the stratum germinativum, or between the stratum germinativum layer of cells, and the dermis. It is popularly believed that these clear cells take origin from the neuro-ectoderm, ie. that they are fine Schwann cell sheaths that terminate in special endings at the dermal-epidermal junction.

What is the effective stimulus for the production of melanin? Under suitable stimulus (MSH? – Fig. II) the aforementioned clear cell is converted to a melanoblast. In the latter, the amino-acid tyrosine, obtained from the blood, is converted to a DOPA-like substance (*dioxyphenyl alanin* was the experimental chromogen used; the real chromagen is not thought to be precisely the same), and then under the action of DOPA-oxidase melanin is produced. The various accelerating (——→) and inhibiting (-+++++++→) factors are shown as they are believed to work. The resulting brown to black melanin granules impart to the skin a brown colour, except in the Mongol, where sheer distance from the skin produces a bluish discolouration. The albino, on the other hand, is unable to produce any melanin.

Patho-Physiology

Melanoblasts can be found in the entire surface epithelium and the mucosa of the buccal cavity, esophagus and urethra. They are classified as to five types: *junctional, compound, intradermal, juvenile* and *blue.* Before puberty, the melanoblasts which lie in the lower layers of the epidermis at the junction of the dermis, undergo a benign proliferation giving rise to the pigmented *junctional nevus* or *melanoma.* By puberty, about 90% of these have migrated down into the dermis to become *intradermal* nevi, but there will be a time of course when these cells lie both in the epidermis and dermis, and are at that time regarded as a *compound* nevus. After puberty therefore, just over 10% of moles lie above the dermis, and these are the dangerous ones, for malignancy almost always arises from a junctional nevus or the junctional component of a compound nevus.

Clinically, the junctional nevus may infiltrate through all layers of the epidermis, being somewhat surreptious in behaviour, for quite often the main island of cells is surrounded by marginal satellites of much smaller groups of melanoblasts,

separated by normal epidermal tissue. The junctional type occur as light to dark brown spots varying in size from a millimetre to several centimetres, and being smooth and non-hairy. They are commonly located on palms of hands, soles of feet and external genitalia, from whence their prophylactic removal is urged. As pointed out, this is the variety that commonly partakes in metaplasia to form malignant melanoma, illustrating histologically, increased mitotic activity, increase in size of nucleus wth anaplasia, and cellular hyperchromatism.

The compound melanoma, clinically, is once again variable in size, from a millimetre to several centimetres, and varying in colour from light to dark brown. These, however, are flat and smooth or, papillary and hairy, and these same clinical features apply precisely to the intradermal nevus, whose location really represents the mature migration of melanoblastic cells. This type may be found extensively throughout the dermis, even extending into the subcutaneous fat. It is *never* located on palms, soles or genitalia.

The *juvenile nevus* has been regarded as an entity for less than fifteen years now, and is one found before puberty and pursuing a benign course, but exhibiting a bizarre histological pattern, suggestive of malignancy (ie. occurrence of fusiform spindle-shaped cells plus giant cells). Its importance lies in the fact that malignant melanoma is rare in children, and any nevus which may be sectioned and which exhibits features of metaplasia should not tempt one to treat it radically for it will in all probability turn out to be quite benign.

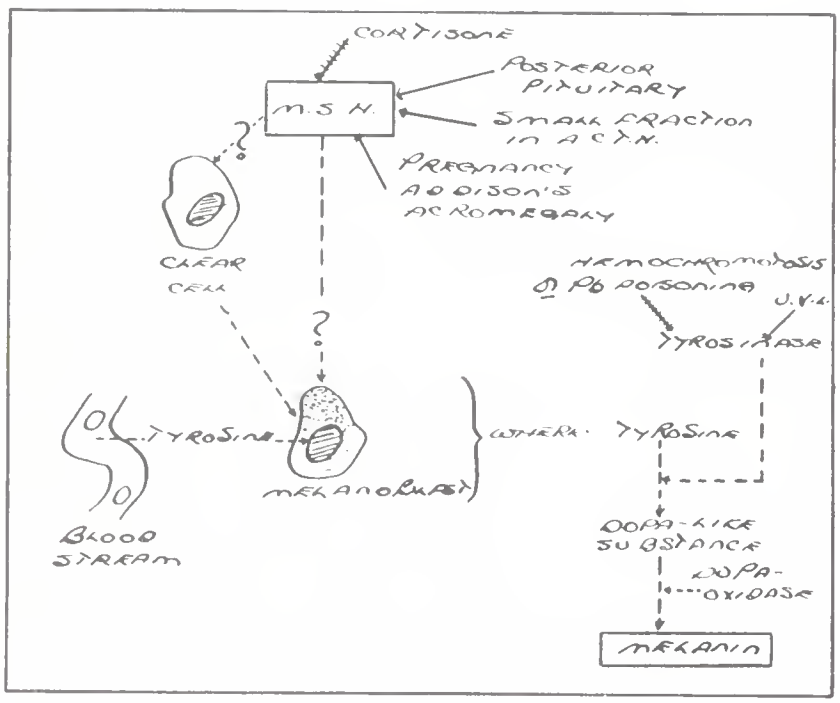

Fig. II

Earlier in the discussion, it was mentioned that almost all melanin found in the dermis resides in chromatophores. One exception to this is the *blue nevus* which is thought to be derived from the Schwannian sheath cells of dermal nerves, and which resides purely in the dermis, never possessing an epidermal component. This is commonly seen on the face, dorsum of the hands and feet, and over the sacrum in all members of the Mongolian race. It remains benign in all but a few cases.

It is now auspicious to briefly consider what may stimulate a previously quiescent benign nevus to malignancy. As with all phases of cancer, no real etiology is known, but the importance of two searching questions has preoccupied researchers: *endocrine* and *traumatic* factors.

Endocrine. When one examines the hormonal influences in Fig. II, it is not surprising to realize that an upset in this branch of the "interne milieu" could promote malignancy. For example, why are children, who possess the histologically-prone type of nevus to develop metaplasia, so well protected against malignancy up to puberty? Does the distribution of pigmention in Addison's disease reflect a semi-malignant change? Can the same be said of the pigmentation seen in pregnancy in the areola and linea nigra? Specific answers to these questions are not known but it is felt that in children there is an inhibiting hormonal factor which makes malignant melanoma a rarity. And yet conversely, it can be said as a result of observation that treatment with steroids, or by adrenalectomy, hypophysectomy or oophorectomy appears to exert little effect in reversing the course of a malignant melanoma.

Trauma. This is mentioned with reference to the practice of prophylactic removal of moles at an early age, acting as a trigger for malignant change. Suffice it to quote Sir Stanford Cade: "There is no evidence that trauma, whatever its kind, has the power to transform a benign pigmented lesion into a malignant melanoma".[1]

Clinically

The physician should maintain a high degree of *suspicion* concerning malignant melanoma in a patient who complains of, or notices, with reference to a nevus:

Satellite nevi or halo
Ulceration
Sanguinity (ie. bleeding or increased vascularity)
Painful, tender
Itching
Concentrated sunlight producing blistering
Increase in size or depth of colour (brown to black)
Oozing or crusting
Newly discovered pigmented lesion in an adult

The frequency with which various areas of the body become affected by primary melanoma is illustrated in Fig. III.

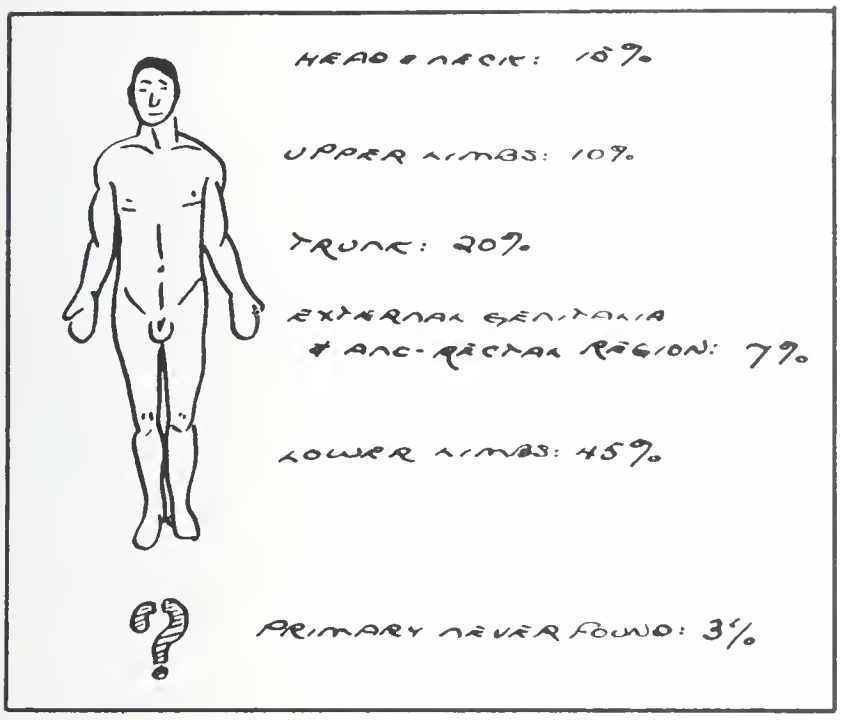

Fig. III

The diagnosis of malignant melanoma rests solely on microscopic examination of suspect tissue which if typical melanocarcinoma shows the usual criterion of malignancy — cellular pleomorphism, increase in nuclear size with anaplasia, abundance of mitosis and invasion of both dermis and epidermis. Accordingly, George, Fortner and Pack have classified the stages of the disease thusly:

I — disease localized to the primary site
I (a) — disease recurrent locally, or in which immediate regional spread is evident
II — regional lymph nodes contain metastatic melanoma
III — metastatic melanoma is beyond regional confines

The primary spreads therefore especially by lymphatics (permeation leading to local lymph channel involvement; direct extension producing node involvement), and bloodstream. Few tumors are so unpredictable as to their timing, mode and result of spread.

Treatment

Management of malignant melanoma can be considered as might be expected, under surgery, radiotherapy and chemotherapy. Many factors will determine the success or failure of each or all of these, not the least important of which is the stage of disease being treated. It could be said that in most instances surgery is recommended, and the other two therapeutic measures are used as adjuvant treatment. Surgery should consist of: i) wide local three-dimensional excision at the earliest moment, the excision requiring a skin graft to close it; ii) prophylactic block dissection and removal of lymph nodes if they be in contact with the primary operative site; iii) block dissection and removal of lymph nodes which become involved with malignancy subsequent to a primary operation; iv) complete amputation of a limb as a primary measure in certain selected patients, or as palliative treatment in advanced cases.[2]

Contrary to earlier belief, radiotherapy is of certain value in management of this disease, but it should never be chosen as an alternative to surgery, where surgery is indicated. Indications for radiotherapy are: i) prophylactically as a post-operative measure; ii) in the treatment of an irremovable growth; iii) when advanced age or site and extent of tumor precludes adequate removal; iv) as a palliative measure.[3]

Chemotherapy offers the greatest promise for the future in the handling of malignant melanoma, but as yet is still much in the neophytic stage. The utilization of two agents in particular is suggested, which can be effected in a variety of ways: i) pre-operative nitrogen-mustard intravenously, or Melphalan (alkylating agent) per os; ii) post-operative maintenance following excision, with Melphalan per os; iii) regional extra-corporeal perfusion of a limb using large doses of nitrogen-mustard or Melphalan in patients with advanced disease, site localized to one limb; iv) systemic infusion of Melphalan in the case of generalized metastatic dissemination.[4]

Malignant melanoma is not as common nor any more lethal than the gastro-intestinal malignancies. The five year survival rate is affected by the stage of disease treated, sex (females have a better response than males), and mode of treatment, but generally is regarded overall as 40%, with

25% being disease free.5 However, the very fact that this neoplasm is visible to the naked eye, and that it can be seemingly wiped out only to reappear elsewhere at a later date, is probably responsible for the horror which surrounds both the physician's and patient's individual interpretation of the "Black Cancer".

ACKNOWLEDGEMENT:—My appreciation is extended to Drs. Wm. Anderson, N. A. Watters, and N. M. Wrong, for stimulation in past teaching of this subject.

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ABSTRACT: *Hysteria — The Stability and Usefulness of Clinical Criteria: a Quantitative Study Based on a Followup Period of Six to Eight Years in 39 Patients;* Perley and Guze; N. Eng. Journal of Medicine, March 1, 1962, vol. 266, no. 9, pp. 421-426.

Hysteria is seen as a distinct syndrome by these workers. It is generally found in women with its onset being in early life. The diagnosis of hysteria must be made according to specific criteria, in order that medical, neurological, and psychiatric possibilities not be overlooked.

Criteria have been established by the Washington University psychiatric clinic for retrospective diagnosis of hysteria. A dramatic or complicated medical history often begins in these patients before the age of thirty-five. A minimum of 15 discrete symptoms distributed in 9 of 10 specified groupings is part of the picture of hysteria. These symptoms include vague, diverse complaints, multiple pains, numerous sexual symptoms as dysmenorrhea, dyspareunia and frigidity, a history of excessive hospitalization and surgical operations, nervousness, fears, depressed feelings and thinking of dying or suicide. In the cases considered, no other diagnosis could have been made to explain the symptoms.

Hysteria, then, as defined by this particular investigation, is a syndrome recognizable by means of the usual clinical methods using specific criteria.

S.J.G.

UPJOHN ABSTRACT: *Chemotherapy of Advanced Ovarian Cancer;* Vaitkevicius, Talley, Brennan, et al.; J. Mich. Med. Soc. 60:492-496 (April) 1961.

This is a review of experience with 60 patients with advanced ovarian cancer, some of whom were treated with uracil mustard.

Certain general conclusions were drawn from this study. The course of ovarian carcinoma is unpredictable; long-term survivals without therapy have occurred despite dissemination of the disease. Systematic chemotherapy is indicated only when there is actively progressive and symptomatic disease. In about 1/3 to ½ of the patients with advanced ovarian cancer may one expect to relieve symptoms effectively; some prolongation of life may be possible. The average survival after the appearance of symptoms was 13.2 months in 26 systematically treated patients responding to chemotherapy, 6.5 months in patients not responding to systematic therapy, and 5.6 months in patients treated locally.

Chlorambucil and cyclophosphamide appear to be the drugs of choice at this time in the treatment of ovarian cancer. They are preferred because of their relative safety and ease of oral administration, not because of any greater efficacy. There seems to be cross-resistance between the different radiomimetic drugs. Patients resistant to radiomimetic drugs may sometimes be treated effectively with drugs having a different mechanism of action, such as 5-fluorouracil and vincaleukoblastine.

Diagnostic Radiology

Answers to Questions from page 220, 221

Figure 1. Fracture of Scaphoid

This fracture occurs most commonly in young adults and is usually sustained by a fall on the outstretched hand. The fracture nearly always occurs through the middle or waist of the bone, both fragments thus being of about equal size. Rarely is there any appreciable displacement of the fragments and often the patient can carry on the use of his hand because pain is slight. Increased pain may only be noticed on strong handshakes, heavy lifting, or accidental bangs on the dorso-radial aspect of the wrist, in cases not diagnosed early.

When a patient reports early after the injury, it is essential to take anteroposterior, lateral, and two oblique views of the wrist. Sometimes stereo views of the scaphoid bone are also taken. Often the fracture line will be so fine as to not be seen in the first radiographs and, in such case, radiographic examination should be repeated in two weeks. Meanwhile it is wise to immobilize the wrist in plaster, both to rest the wrist and to ensure the patient's return.

The most frequent complications, of which there is a high incidence in fractures of the scaphoid bone, are delayed union, non-union, and osteoarthritis.

Figure 2. Pott's Fracture

The general term Pott's fracture is used frequently to describe any fracture-dislocation of the ankle. Actually there are many specific different types of fractures and fracture-dislocations of the ankle. This one is described as a tri-malleolar fracture with posterior dislocation of the talus. Both malleoli and the posterior margin of the tibia are fractured.

This lady's fracture-dislocation was reduced satisfactorily with manipulation under anaesthesia, and below-knee cast was applied. Often, either it is impossible to obtain a satisfactory reduction by manipulation, or dislocation recurs in plaster as soft tissue swelling diminishes. This necessitates resort to operative reduction and fixation by screw or screws. The ankle is protected in plaster then for ten to twelve weeks before mobilizing exercises are begun.

Figure 3. Intravenous Pyelogram

Note that no dye is being excreted by the left kidney, indicating non-function.

On the right side there is increased size of the kidney pelvis and blunting of the calyceal angles, indicating hydronephrosis. The enlarged diameter of the ureter shows that hydroureter is also present. Since no dye is reaching the bladder, there must be obstruction of the ureter. From the level of the obstruction, it would appear to be at or in the bladder wall.

Figure 4. Osteogenic Sarcoma

This malignant tumour of childhood or early adult life arises in the metaphysis of a bone from primitive bone-forming cells. The upper end of humerus is one of the common sites, as are the lower end of femur and upper end of tibia.

Radiographs show irregular destruction of the metaphysis, giving it a moth-eaten appearance. Biopsy confirms the diagnosis.

Treatment was by forequarter amputation, ie. through a site well clear of the tumour.

Figure 5. Mestatic Osteogenic Sarcoma

This is the same young lady as in Figure 4, two years after amputation of her right arm. A huge cannon-ball metastasis was found in her left chest. Pulmonary mestases are common in this disease and cause the mortality rate to be 85% even after amputation.

The opponents of early amputation feel that metastases have occurred by the time of diagnosis and therefore it would be preferable to use radiotherapy in heavy dosage followed by a period of observation. If there are no metastases found after six months or a year, then the limb may be amputated with some hope of permanent cure and thus the psychological trauma of a fruitless amputation will have been avoided.

Figure 6. Excretory Urogram

In this case the bladder never filled completely. There is a large irregular filling defect in the region of the bladder neck. A bladder diverticulum is projecting to the right and considerable trabe-

culation is present. In the post void film there was incomplete emptying of the bladder. The plain film showed a large soft tissue shadow in the supra pubic region. Thus, the opinion of the radiologist was that the above findings were caused by a considerable enlargement of the prostate.

Figure 7. Prostatic Calcifications

The innumerable tiny calcifications within the substance of the prostate gland may be seen through the pubis. This is suggestive of previous prostatic infection.

Figure 8. Aortic Aneurysm

Ten years before her death, this patient was discovered to have syphilis and luetic aortic aneurysm was suspected. From six to three weeks before death, she had gradual onset of dyspnoea and noisy breathing. A large aneurysm of the arch of aorta, compressing the trachea, was diagnosed and a bypass operation was undertaken. Post-operative complications led to death.

At autopsy, a large spherical aneurysim of the distal arch of aorta, compressing all structures in front and eroding vertebrae behind, was found. These findings can be seen in this lateral view.

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